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(54) **3,6-Disubstituted pyridazine derivatives.**

(57) A 3,6-disubstituted pyridazine derivative having excellent platelet agglutination inhibitory effects. It is useful for a preventive medicine or a therapeutic medicine for a cerebrovascular disorder such as cerebral thrombosis and cerebral embolism, an ischemic heart disease such as myocardial infarction, and a circulation disorder such as a peripheral circulation disorder. A pharmaceutical composition containing a composition of the present invention as an effective ingredient and a process for preparing the same are also disclosed.

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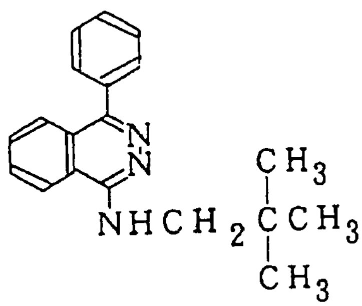
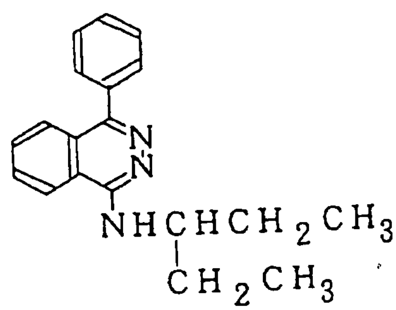
The present invention relates to 3,6-disubstituted pyridazine derivatives and, more particularly- to 3,6-disubstituted pyridazine derivatives which have platelet agglutination inhibitory action and, hence, are useful as a preventive medicine or a therapeutic medicine for a cerebrovascular disorder such as cerebral thrombosis and cerebral embolism, an ischemic heart disease such as myocardial infarction, and a circulation disorder such as a peripheral circulation disorder. The present invention also relates to optical antipodes of such 3,6-disubstituted pyridazine derivatives and pharmaceutically acceptable acid-addition salts thereof.

Most cerebrovascular disorders such as cerebral thrombosis and cerebral embolism, ischemic heart diseases such as myocardial infarction, and circulation disorders such as a peripheral circulation disorder are caused by a thrombus which is produced in a blood vessel and which occludes the blood vessel. Such a thrombus is produced mainly because platelets agglutinate in the earlier stage of the formation of the thrombus.

As compounds having a platelet agglutination inhibitory action, various 4-phenylphthalazine derivatives are conventionally known. For example, Japanese patent Laid-Open Nos. 53659/1981, 53660/1981 and 48972/1982 disclose 1-anylino-4-phenylphthalazine derivatives, and Japanese Patent Laid-Open Nos. 218377/1985 and 243074/1985 disclose the compounds represented by the following general formulas (II) and (III), respectively, as compounds having a strong platelet agglutination inhibitory action in vitro:



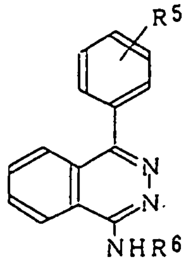
... (II)



... (III)

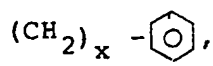
These compounds, however, show almost no platelet agglutination inhibitory action whey they are administered orally, or the platelet agglutination inhibitory action in vivo cannot be said to be satisfactory.

British patent No. 1303016, Journal of Medicinal Chemistry, 12,555 (1969), etc. disclose 1-amino-4-phenyl-phthalazine derivatives represented by the following general formula (IV):



... (IV)

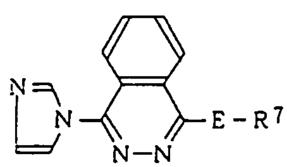
wherein R^5 represents a hydrogen atom or a chlorine atom, R^6 represents an alkyl group having 1 to 3 carbon atoms, $-(CH_2)_yN(CH_3)_2$, wherein y represents 2 or 3, a cyclohexyl group, or



wherein x represents 1 or 2.

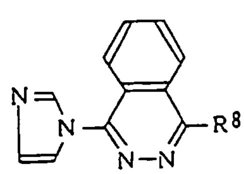
However, the compounds concretely disclosed have a restricted structure, and only an anti-inflammatory action and an anti-rheumatoid action are described as the pharmaceutical effects thereof.

As phthalazine derivatives having a non-substituted imidazole group at the fourth position, Japanese Patent Laid-Open Nos. 129180/1990, 129181/1990, 129182/1990 and 129183/1990 disclose compounds represented by the following general formulas (V) to (VIII), respectively:



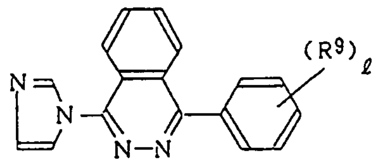
... (V)

wherein E represents -NH-, -O- or -S-, and R^7 represents a straight-chain or branched-chain alkyl group having 1 to 18 carbon atoms, a straight-chain or branched-chain alkyl group having 2 to 4 carbon atoms containing a hydroxyl group, an allyl group, a 3-methoxypropyl group, a tetrahydrofurfuryl group, a furfuryl group, a benzyl group which may be substituted by a chlorine atom or an alkyl group, or a phenyl group which may be substituted by a phenethyl group, a pyridylmethyl group or a chlorine atom, provided that when E is -NH-, R^7 is not a substituted or non-substituted phenyl group;



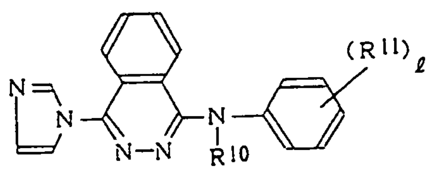
... (VI)

wherein R^8 represents a lower alkoxyphenyl group, an allyloxyphenyl group, a pyridylmethyloxyphenyl group, a furyl group which may have a substituent, a thienyl group which may have a substituent, or a naphthyl group which may have a substituent;



... (VII)

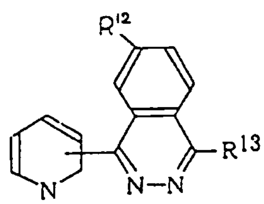
wherein R^9 which may be the same or different from each other represents a hydroxyl group, a lower alkyl group, a methoxy group, an acetylamino group, a halogen atom, a methylthio group or an ethoxycarbonylvinyl group, and ℓ represents an integer of 0 to 3; and



... (VIII)

wherein R^{10} represents a hydrogen atom, a lower alkyl group, R^{11} which may be the same or different from each other represents a hydroxyl group, an alkyl group having 1 to 5 carbon atoms, a lower alkoxy group, an acylamino group, a halogen atom, a cyano group, a nitro group, an anmino group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkylcarbonyl group or an alkylthio group, and ℓ represents an integer of 0 to 3.

As a phthalazine derivative having a non-substituted pyridyl group at the fourth position, Japanese patent Laid-Open No. 106873/1991 discloses a compound represented by the following general formulas (IX):

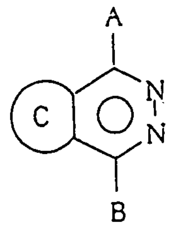


... (IX)

wherein R^{12} represents a hydrogen atom or a methoxy group, and R^{13} represents $-NR^{14}R^{15}$, wherein R^{14} represents an alkyl group, a phenyl group which may be substituted by a halogen atom or a cyano group, or a pyrimidinyl group which may have a substituent, and R^{15} represents a hydrogen atom or a lower alkyl group, or R^{14} and R^{15} may combine to form a piperidino group, a piperazino group, a morpholino group or an imidazolyl group.

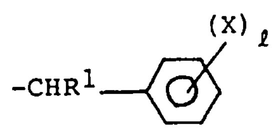
As a result of studies of pyridazine derivatives having excellent platelet agglutination inhibitory action, the present inventors have found that 3,6-disubstituted pyridazine derivatives satisfy the above-described requirements. The present invention has been achieved on the basis of this finding.

The present invention provides 3,6-disubstituted pyridazine derivatives represented by the following general formula (I), optical antipodes thereof and pharmaceutically acceptable acid-addition salts thereof:

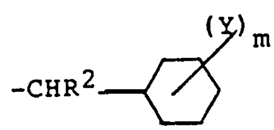


... (I)

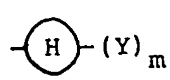
wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a phenyl group, a thienyl group, a furyl group, a thiazolyl group, a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms, a phenylthio group, a nitrogen-containing saturated cyclic group, a pyridyl group or an imidazolyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



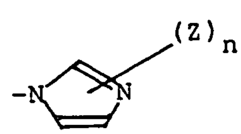
(wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents an integer of 0 to 3),



(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6);

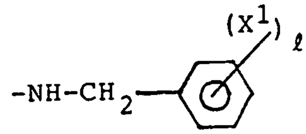


(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cycloalkyl group having 5 to 8 carbon atoms or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or



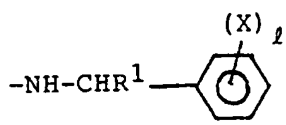
(wherein Z independently represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 to 2); and the ring C represents a benzene ring; a furan ring; or a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms,
provided that the following compounds (1) to (4) are excluded:

(1) compounds represented by the formula (I) wherein A represents a non-substituted imidazolyl group, the ring C represents a benzene ring, and B represents



(wherein X_1 independently represents a halogen atom or an alkyl group having 1 to 4 carbon atoms, and ℓ is as defined above), or an alkylamino group having 3 to 8 carbon atoms;

(2) compounds represented by the formula (I) wherein A represents a phenyl group which may have a substituent, the ring C represents a benzene ring, and B represents



(wherein R^1, X and ℓ are as defined above);

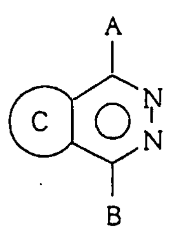
(3) compounds represented by the formula (I) wherein A represents a non-substituted phenyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon atoms; and

(4) compounds represented by the formula (I) wherein A represents a pyridyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon atoms.

The present invention also provides a pharmaceutical composition containing, as an active ingredient, a 3,6-disubstituted pyridazine derivative of the above formula (I), an optical antipode thereof and a salt thereof.

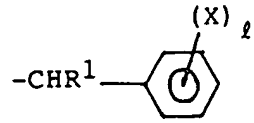
The present invention also provides a process for the preparation of a 3,6-disubstituted pyridazine derivative of the above formula (I), an optical antipode thereof or a salt thereof.

Compounds according to the present invention are 3,6-disubstituted pyridazine derivatives represented by the following general formula (I), optical antipodes thereof and pharmaceutically acceptable acid-addition salts thereof:

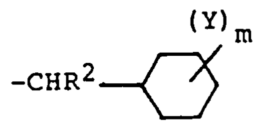


... (I)

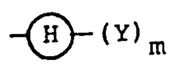
wherein A represents an alkyl group having 3 to 6 carbon atoms (e.g., propyl group and hexyl group); a cycloalkyl group having 5 to 7 carbon atoms (e.g., cyclopentyl group and cycloheptyl group); a phenyl group, a thienyl group (e.g., 2-thienyl group and 3-thienyl group), a furyl group (e.g., 2-furyl group and 3-furyl group), a thiazolyl group (e.g., 2-thiazolyl group), a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms (e.g., benzyl group and phenylpropyl group), a phenylthio group, a nitrogen-containing saturated cyclic group (e.g., pyrrolidino group, piperidino group and morpholino group), a pyridyl group (e.g., 2-pyridyl group and 3-pyridyl group), or an imidazolyl group (e.g., 1-imidazolyl group and 2-imidazolyl group) each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms (e.g, methyl group and butyl group), an alkoxy group having 1 to 4 carbon atoms (e.g., methoxy group and butoxy group) and a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom and iodine atom); B represents -NH-D [wherein D represents



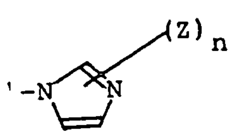
(wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms (e.g., methyl group and butyl group), X independently represents a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom and iodine atom), an alkyl group having 1 to 4 carbon atoms (e.g., methyl group and butyl group) or an alkoxy group having 1 to 4 carbon atoms (e.g., methoxy group and butoxy group), and ℓ represents an integer of 0 to 3),



(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms (e.g., methyl group and butyl group), Y independently represents an alkyl group having 1 to 4 carbon atoms (e.g., methyl group, butyl group) or an alkoxy group having 1 to 4 carbon atoms (e.g., methoxy group and butoxy group), or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms (e.g., methylene group and propylene group) which may be substituted by an alkyl group having 1 to 3 carbon atoms (e.g., methyl group and propyl group), and m represents an integer of 0 to 6),

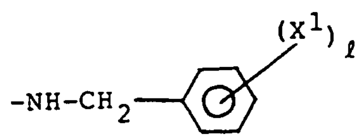


(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms (e.g., cyclopentyl group and cycloheptyl group), and Y and m represent are as defined above), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms (e.g., methyl group, propyl group and pentyl group), and R^4 represents a cycloalkyl group having 5 to 8 carbon atoms (e.g., cyclopentyl group and cyclooctyl group) or a thienyl group (e.g., 2-thienyl group and 3-thienyl group)), or an alkyl group having 3 to 8 carbon atoms (e.g., propyl group, pentyl group and octyl group)]; or



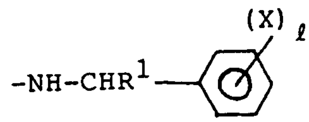
(wherein Z independently represents an alkyl group having 1 to 4 carbon atoms (e.g., methyl group and butyl group) or a phenyl group, and n represents an integer of 0 to 2); and the ring C represents a benzene ring; a furan ring; or a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms (e.g., methyl group and butyl group), provided that the following compounds (1) to (4) are excluded:

(1) compounds represented by the formula (I) wherein A is a non-substituted imidazolyl group, the ring C is a benzene ring, and B is



(wherein X_1 independently represents a halogen atom or an alkyl group having 1 to 4 carbon atoms, and ℓ is as defined above) or an alkylamino group having 3 to 8 carbon atoms;

(2) compounds represented by the formula (I) wherein A is a phenyl group which may have a substituent, the ring C is a benzene ring, and B is



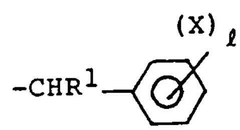
(wherein R^1, X and ℓ are as defined above);

(3) compounds represented by the formula (I) wherein A is a non-substituted phenyl group, the ring C is a benzene ring, and B is an alkylamino group having 3 to 8 carbon atoms; and

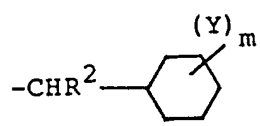
(4) compounds represented by the formula (I) wherein A is a pyridyl group, the ring C is a benzene ring, and B is an alkylamino group having 3 to 8 carbon atoms.

Among these, examples of preferable compounds are:

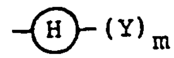
(1) compounds represented by the formula (I) wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a thienyl group, a furyl group, a thiazolyl group or a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms, a phenylthio group, a nitrogen-containing saturated cyclic group or an imidazolyl group, each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 3 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



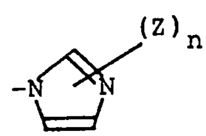
(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X and ℓ represent the same as defined above,



(wherein R^2, Y and m are as defined above),



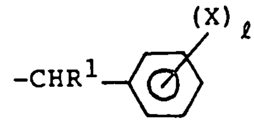
(wherein the ring H, Y and m are as defined above), or an alkyl group having 3 to 8 carbon atoms]; or



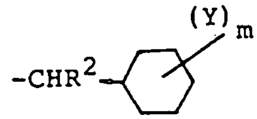
(wherein Z and n are as defined above); and the ring C represents a benzene ring;

(2) compounds represented by the formula (I) wherein A represents a phenyl group which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents $-CHR^3R^4$ (wherein R^3 and R^4 are as defined above)]; and the ring C represents a benzene ring; and

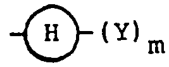
(3) compounds represented by the formula (I) wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a phenyl group, a thienyl group or a pyridyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 3 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



(wherein R^1, X and ℓ are as defined above);

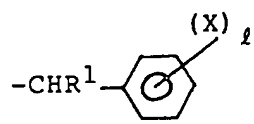


(wherein R^2, Y and m are as defined above); or

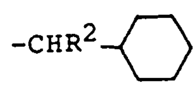


(wherein the ring H, Y and m are as defined above)]; and the ring C represents a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms.

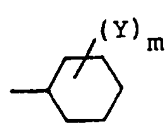
As examples of more preferable compounds will be cited compounds represented by the formula (I) wherein A represents a phenyl group which may be substituted by an alkyl group having 1 to 4 carbon atoms, a chlorine atom or an alkoxy group having 1 to 4 carbon atoms; an alkyl group having 3 to 6 carbon atoms; a cyclohexyl group; a thiazolyl group; a phenoxy group; a phenylthio group; a pyrrolidinyl group; a piperidyl group; a morpholinol group; a pyridyl group; a benzyl group which may be substituted by a halogen atom; or a thienyl group, a furyl group or an imidazolyl group each of which may be substituted by an alkyl group having 1 to 3 carbon atoms; B represents -NH-D [wherein D represents



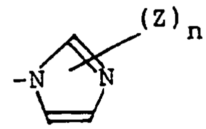
(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X represents a chlorine atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents 0 or 1),



(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms),



(wherein Y independently represents an alkyl group having 1 to 4 carbon atoms or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represent an integer of 0 to 6), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cyclohexyl group or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or

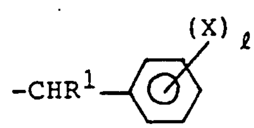


(wherein Z represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 or 1); and the ring C represents a benzene ring, or a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms,
provided that the following compounds (1) and (2) are excluded:

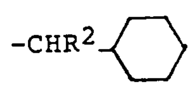
(1) compounds represented by the formula (I) wherein A is a phenyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring; and

(2) compounds represented by the formula (I) wherein A is a pyridyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring.

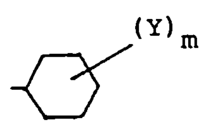
Particularly preferably compounds are, for example, compounds represented by the formula (I) wherein A represents a phenyl group which may be substituted by an alkyl group having 1 to 4 carbon atoms, a chlorine atom or an alkoxy group having 1 to 4 carbon atoms; an alkyl group having 3 to 6 carbon atoms; a cyclohexyl group; a thiazolyl group; a pyrrolidinyl group; a piperidyl group; a morpholinol group; or a thienyl group, a furyl group or an imidazolyl group each of which may be substituted by an alkyl group having 1 to 3 carbon atoms; B represents -NH-D [wherein D represents



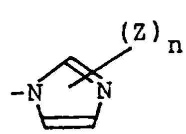
(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X represents a chlorine atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents 0 or 1),



(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms),



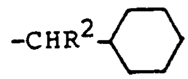
(wherein Y independently represents an alkyl group having 1 to 4 carbon atoms or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represent an integer of 0 to 6), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cyclohexyl group or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or



(wherein Z represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 or 1); and the ring C represents a benzene ring; or a furan ring or a thiophene ring each of

which may be substituted by an alkyl group having 1 to 4 carbon atoms,
provided that compounds represented by the formula (I) wherein A is a phenyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring are excluded.

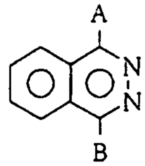
Examples of the most preferable compounds are compounds represented by the formula (I) wherein A represents a phenyl group; or a furyl group or a thienyl group each of which may be substituted by an alkyl group having 1 to 4 carbon atoms, B represents -NH-D [wherein D represents



(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms)], and the ring C represents a benzene ring, or a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms.

Concrete examples of the compounds according to the present invention will be shown in Tables 1 to 5.

Table 1



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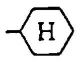
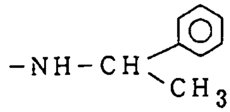
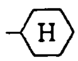
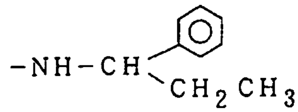
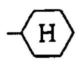
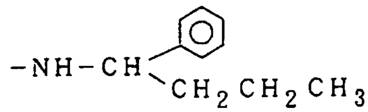
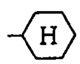
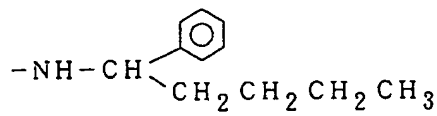
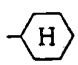
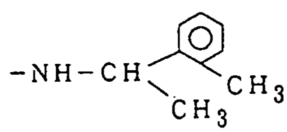
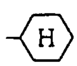
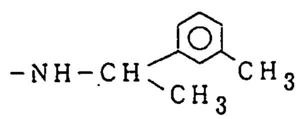
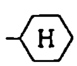
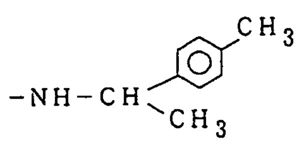
1		
2		
3		
4		
5		
6		
7		

Table 1 (continued)

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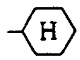
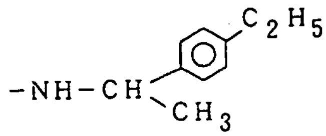
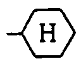
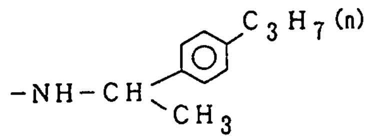
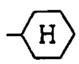
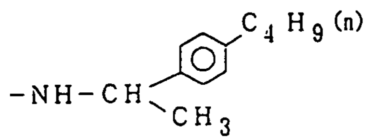
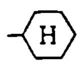
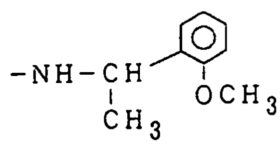
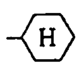
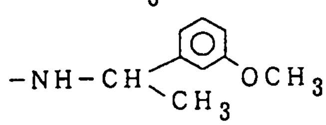
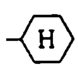
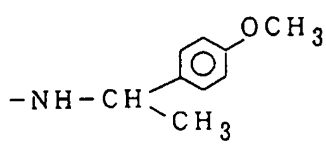
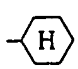
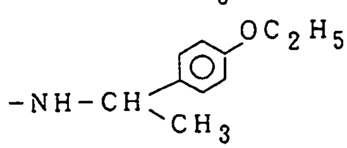
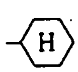
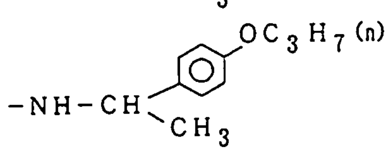
8		
9		
10		
11		
12		
13		
14		
15		

Table 1 (continued)

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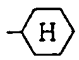
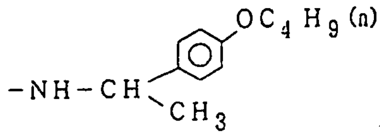
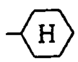
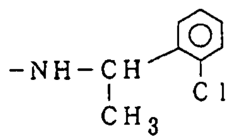
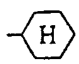
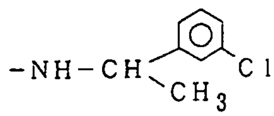
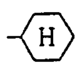
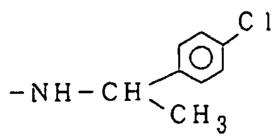
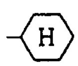
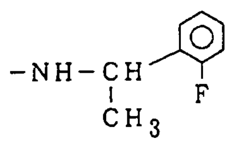
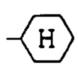
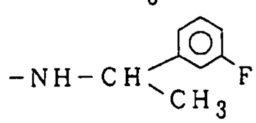
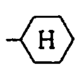
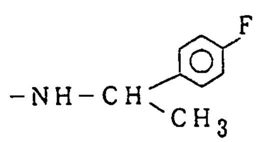
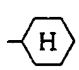
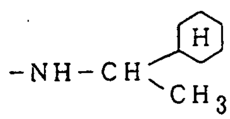
16		
17		
18		
19		
20		
21		
22		
23		

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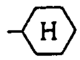
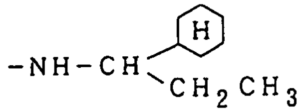
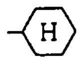
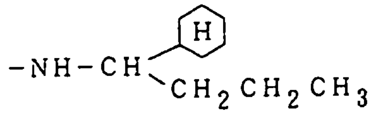
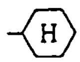
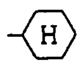
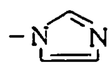
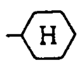
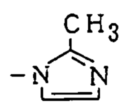
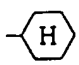
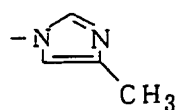
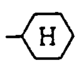
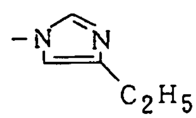
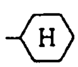
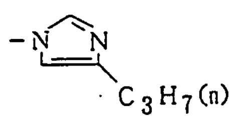
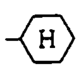
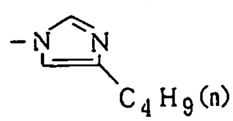
24		
25		
26		
27		
28		
29		
30		
31		
32		

Table 1 (continued)

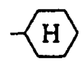
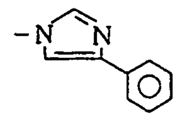
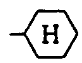
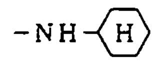
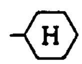
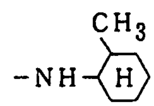
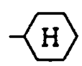
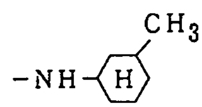
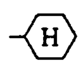
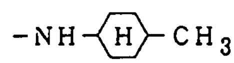
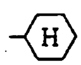
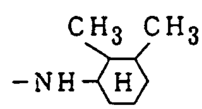
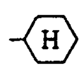
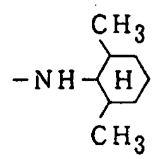
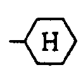
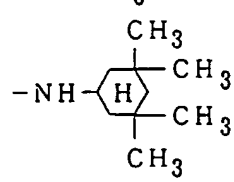
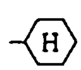
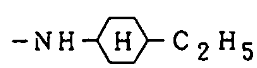
Comp. No.	A	B
33		
34		
35		
36		
37		
38		
39		
40		
41		

Table 1 (continued)

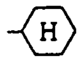
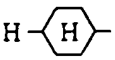
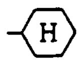
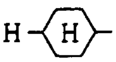
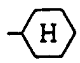
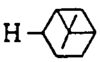
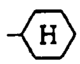
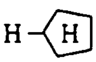
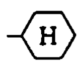
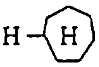
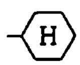
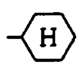
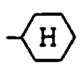
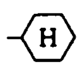
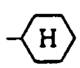
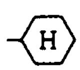
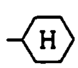
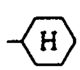
Comp. No.	A	B
42		$-NH-$$-C_3H_7$ (n)
43		$-NH-$$-C_4H_9$ (n)
44		$-NH-$
45		$-NH-$
46		$-NH-$
47		$-NH-(CH_2)_2CH_3$
48		$-NH-(CH_2)_3CH_3$
49		$-NH-(CH_2)_4CH_3$
50		$-NH-(CH_2)_5CH_3$
51		$-NH-(CH_2)_6CH_3$
52		$-NH-(CH_2)_7CH_3$
53		$-NH-CH<^{CH_2CH_3}_{CH_3}$
54		$-NH-CH<^{(CH_2)_2CH_3}_{CH_3}$

Table 1 (continued)

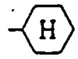
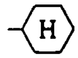
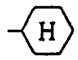
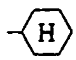
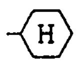
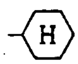
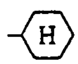
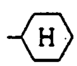
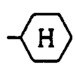
Comp. No.	A	B
55		$-NH-CH(CH_3)-CH(CH_3)_2$
56		$-NH-CH(CH_3)-CH_2-CH(CH_3)_2$
57		$-NH-CH(CH_3)-(CH_2)_3CH_3$
58		$-NH-CH(CH_3)-(CH_2)_4CH_3$
59		$-NH-CH(CH_3)-(CH_2)_5CH_3$
60		$-NH-CH(CH_2CH_3)-CH_2CH_3$
61		$-NH-CH(CH_2CH_3)-CH_2CH_2CH_3$
62		$-NH-CH(CH_2CH_2CH_3)-CH_2CH_2CH_3$
63		$-NHC(CH_3)_3$

Table 1 (continued)

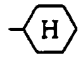
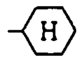
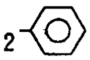
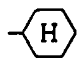
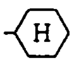
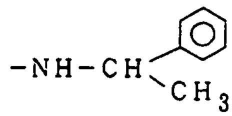
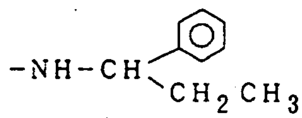
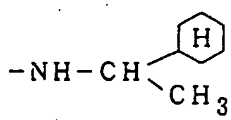
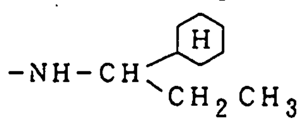
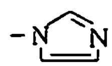
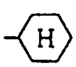
Comp. No.	A	B
64		$-NHCH_2C(CH_3)_3$
65		$-NH-CH_2-$
66		$-NH-CH_2-$
67	$-(CH_2)_2CH_3$	
68	$-(CH_2)_2CH_3$	
69	$-(CH_2)_2CH_3$	
70	$-(CH_2)_2CH_3$	
71	$-(CH_2)_2CH_3$	
72	$-(CH_2)_2CH_3$	$-NH-$
73	$-(CH_2)_2CH_3$	$-NH-CH(CH_2CH_3)CH_2CH_3$
74	$-(CH_2)_2CH_3$	$-NH-CH_2C(CH_3)_3$

Table 1 (continued)

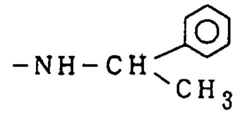
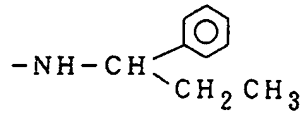
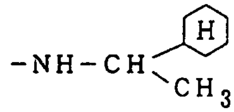
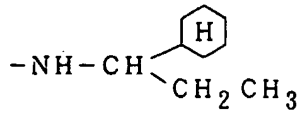
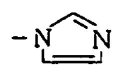
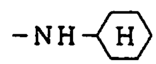
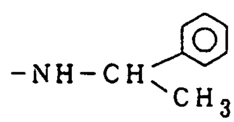
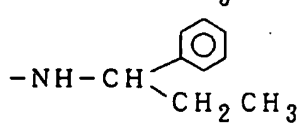
Comp. No.	A	B
75	$-CH(CH_3)_2$	
76	$-CH(CH_3)_2$	
77	$-CH(CH_3)_2$	
78	$-CH(CH_3)_2$	
79	$-CH(CH_3)_2$	
80	$-CH(CH_3)_2$	
81	$-CH(CH_3)_2$	$-NH-CH(CH_2CH_3)_2$
82	$-CH(CH_3)_2$	$-NH-CH_2C(CH_3)_3$
83	$-(CH_2)_3CH_3$	
84	$-(CH_2)_3CH_3$	

Table 1 (continued)

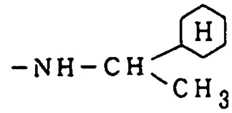
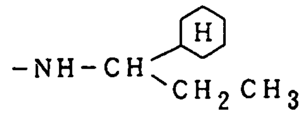
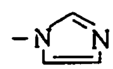
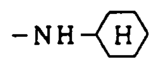
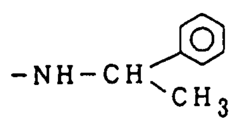
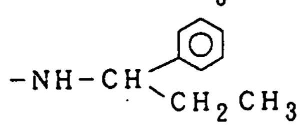
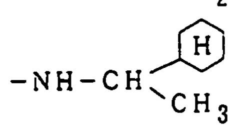
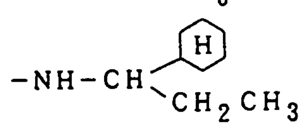
Comp. No.	A	B
85	$-(CH_2)_3CH_3$	
86	$-(CH_2)_3CH_3$	
87	$-(CH_2)_3CH_3$	
88	$-(CH_2)_3CH_3$	
89	$-(CH_2)_3CH_3$	$-NH-CH(CH_2CH_3)(CH_2CH_3)$
90	$-(CH_2)_3CH_3$	$-NH-CH_2C(CH_3)_3$
91	$-C(CH_3)_3$	
92	$-C(CH_3)_3$	
93	$-C(CH_3)_3$	
94	$-C(CH_3)_3$	

Table 1 (continued)

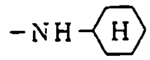
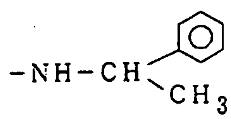
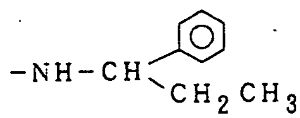
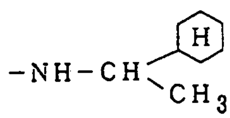
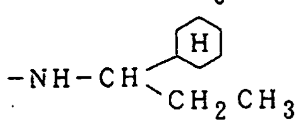
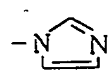
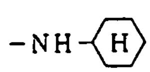
Comp. No.	A	B
95	$-C(CH_3)_3$	
96	$-C(CH_3)_3$	
97	$-C(CH_3)_3$	$-NH-CH(CH_2CH_3)_2$
98	$-C(CH_3)_3$	$-NH-CH_2C(CH_3)_3$
99	$-(CH_2)_4CH_3$	
100	$-(CH_2)_4CH_3$	
101	$-(CH_2)_4CH_3$	
102	$-(CH_2)_4CH_3$	
103	$-(CH_2)_4CH_3$	
104	$-(CH_2)_4CH_3$	
105	$-(CH_2)_4CH_3$	$-NH-CH(CH_2CH_3)_2$

Table 1 (continued)

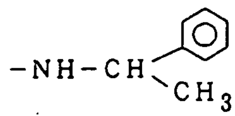
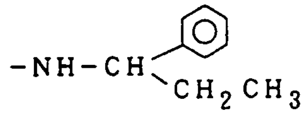
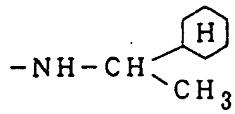
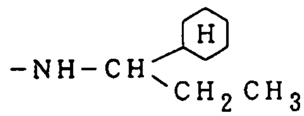
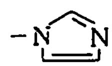
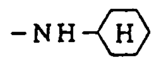
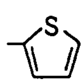
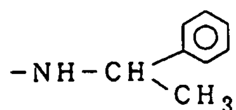
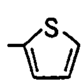
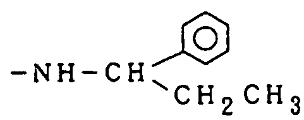
Comp. No.	A	B
106	$-(CH_2)_4CH_3$	$-NH-CH_2C(CH_3)_3$
107	$-(CH_2)_5CH_3$	
108	$-(CH_2)_5CH_3$	
109	$-(CH_2)_5CH_3$	
110	$-(CH_2)_5CH_3$	
111	$-(CH_2)_5CH_3$	
112	$-(CH_2)_5CH_3$	
113	$-(CH_2)_5CH_3$	$-NH-CH\begin{smallmatrix} CH_2CH_3 \\ CH_2CH_3 \end{smallmatrix}$
114	$-(CH_2)_5CH_3$	$-NH-CH_2C(CH_3)_3$
115		
116		

Table 1 (continued)

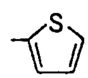
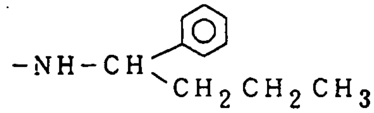
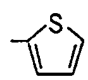
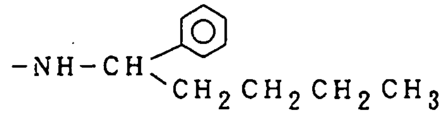
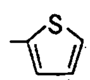
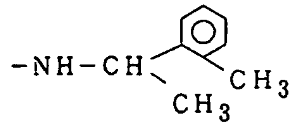
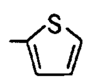
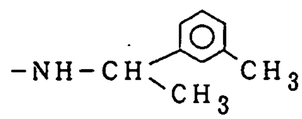
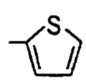
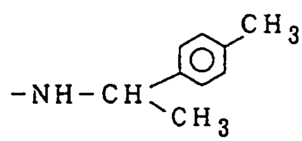
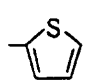
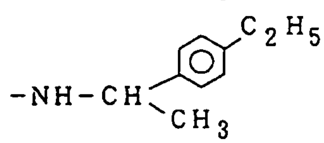
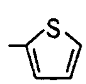
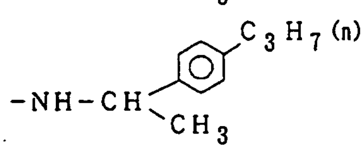
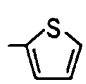
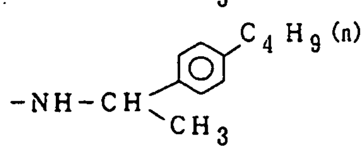
Comp. No.	A	B
117		
118		
119		
120		
121		
122		
123		
124		

Table 1 (continued)

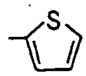
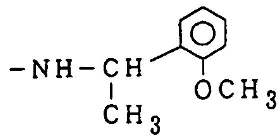
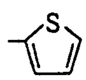
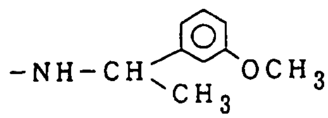
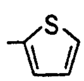
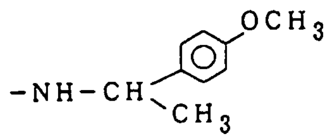
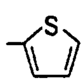
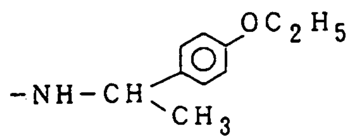
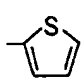
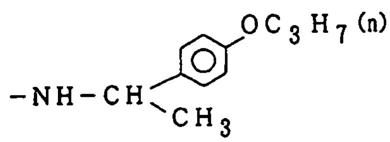
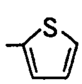
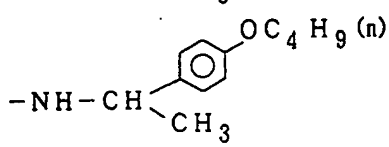
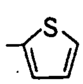
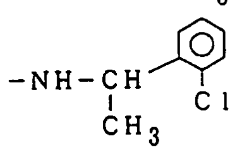
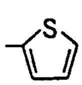
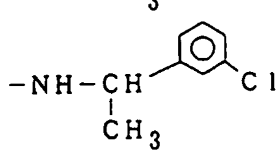
Comp. No.	A	B
125		
126		
127		
128		
129		
130		
131		
132		

Table 1 (continued)

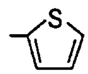
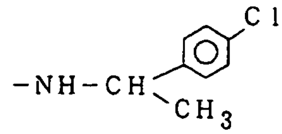
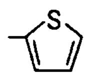
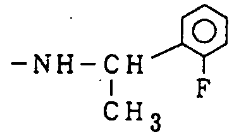
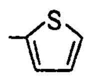
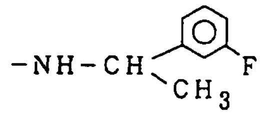
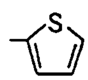
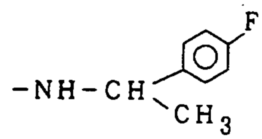
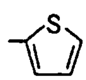
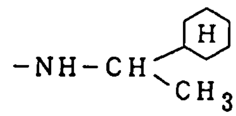
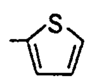
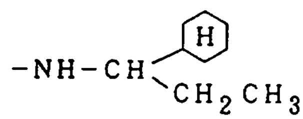
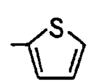
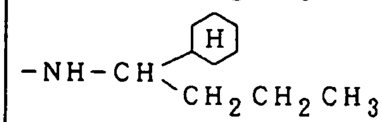
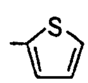
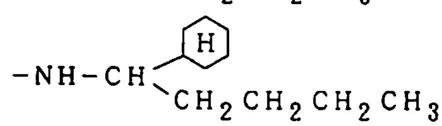
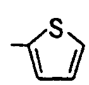
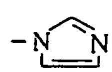
Comp. No.	A	B
133		
134		
135		
136		
137		
138		
139		
140		
141		

Table 1 (continued)

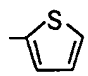
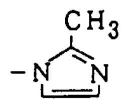
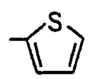
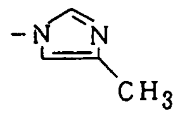
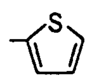
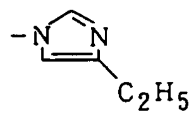
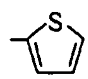
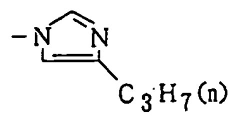
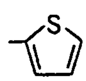
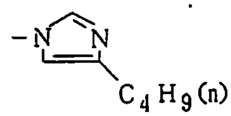
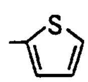
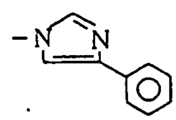
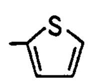
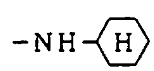
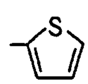
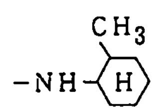
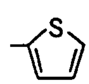
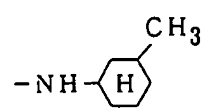
Comp. No.	A	B
142		
143		
144		
145		
146		
147		
148		
149		
150		

Table 1 (continued)

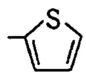
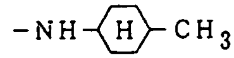
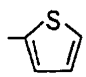
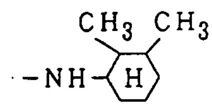
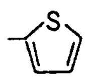
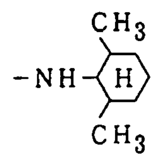
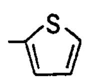
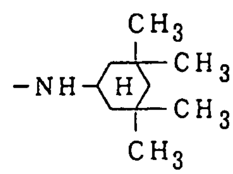
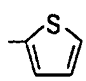
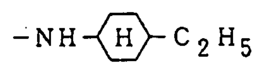
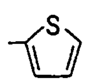
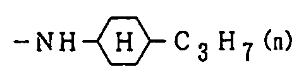
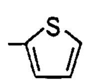
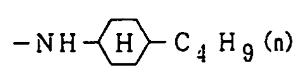
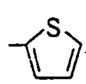
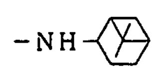
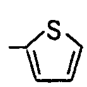
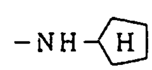
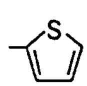
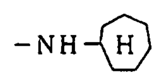
Comp. No.	A	B
151		
152		
153		
154		
155		
156		
157		
158		
159		
160		

Table 1 (continued)

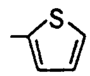
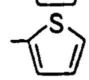
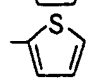
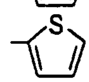
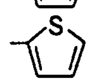
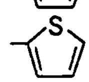
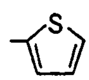
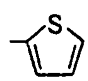
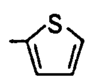
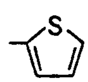
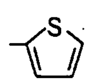
Comp. No.	A	B
161		$-NH-(CH_2)_2CH_3$
162		$-NH-(CH_2)_3CH_3$
163		$-NH-(CH_2)_4CH_3$
164		$-NH-(CH_2)_5CH_3$
165		$-NH-(CH_2)_6CH_3$
166		$-NH-(CH_2)_7CH_3$
167		$-NH-CH{<}\begin{smallmatrix}CH_2CH_3\\CH_3\end{smallmatrix}$
168		$-NH-CH{<}\begin{smallmatrix}(CH_2)_2CH_3\\CH_3\end{smallmatrix}$
169		$-NH-\underset{\substack{\vert\\CH_3}}{CH}-CH(CH_3)_2$
170		$-NH-\underset{\substack{\vert\\CH_3}}{CH}-CH_2-CH(CH_3)_2$
171		$-NH-\underset{\substack{\vert\\CH_3}}{CH}-(CH_2)_3CH_3$
172		$-NH-\underset{\substack{\vert\\CH_3}}{CH}-(CH_2)_4CH_3$

Table 1 (continued)

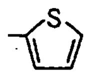
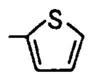
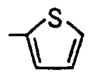
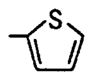
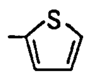
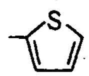
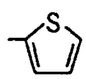
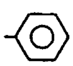
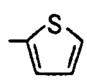
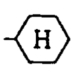
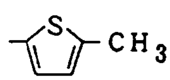
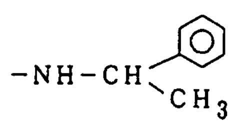
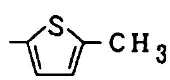
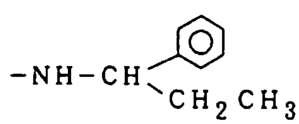
Comp. No.	A	B
173		$-NH-\underset{\mid \atop CH_3}{CH}-(CH_2)_5CH_3$
174		$-NH-\underset{\mid \atop CH_2CH_3}{CH}-CH_2CH_3$
175		$-NH-\underset{\mid \atop CH_2CH_3}{CH}-CH_2CH_2CH_3$
176		$-NH-\underset{\mid \atop CH_2CH_2CH_3}{CH}-CH_2CH_2CH_3$
177		$-NHC(CH_3)_3$
178		$-NHCH_2C(CH_3)_3$
179		$-NH-CH_2-$
180		$-NH-CH_2-$
181		
182		

Table 1 (continued)

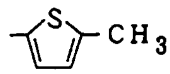
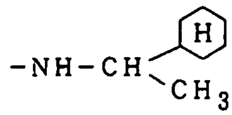
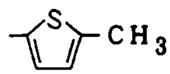
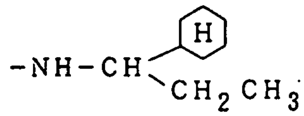
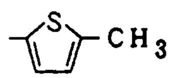
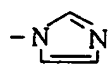
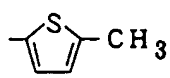
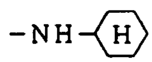
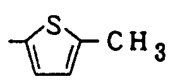
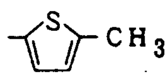
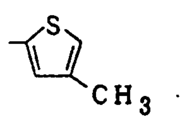
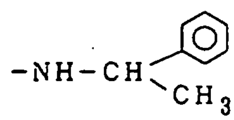
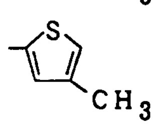
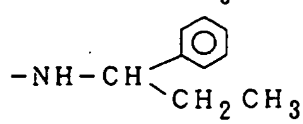
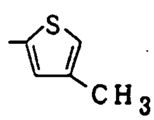
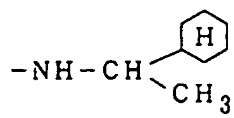
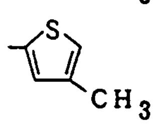
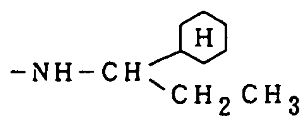
Comp. No.	A	B
183		
184		
185		
186		
187		$-NH-CH(CH_2CH_3)CH_2CH_3$
188		$-NH-CH_2C(CH_3)_3$
189		
190		
191		
192		

Table 1 (continued)

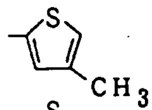
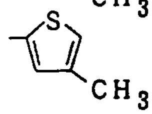
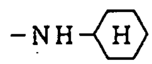
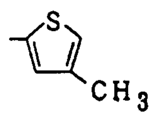
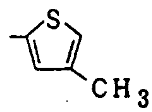
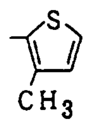
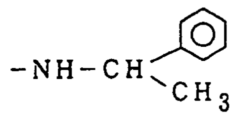
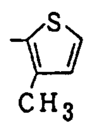
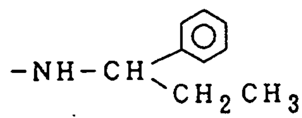
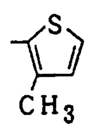
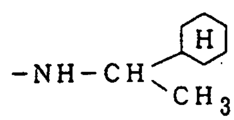
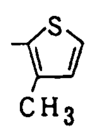
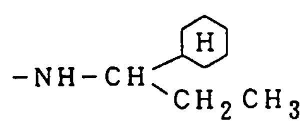
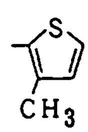
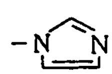
Comp. No.	A	B
193		
194		
195		$-NH-CH(CH_2CH_3)_2$
196		$-NH-CH_2C(CH_3)_3$
197		
198		
199		
200		
201		

Table 1 (continued)

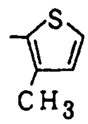
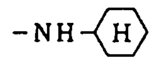
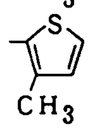
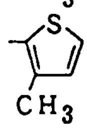
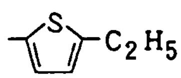
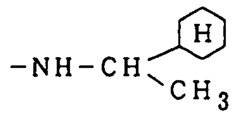
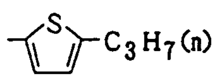
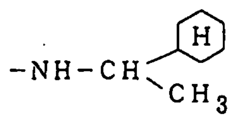
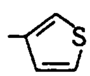
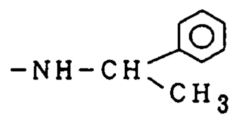
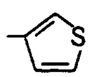
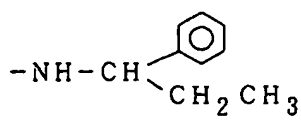
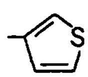
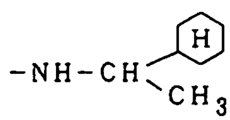
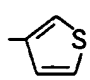
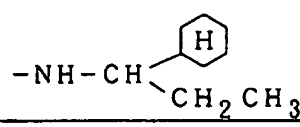
Comp. No.	A	B
202		
203		$-NH-CH\begin{matrix}CH_2CH_3\\CH_2CH_3\end{matrix}$
204		$-NH-CH_2C(CH_3)_3$
205		
206		
207		
208		
209		
210		

Table 1 (continued)

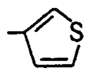
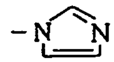
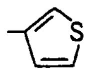
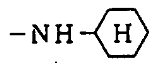
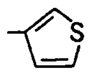
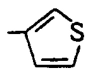
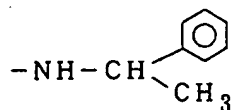
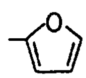
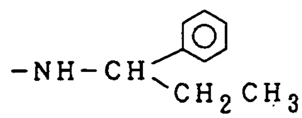
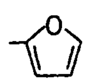
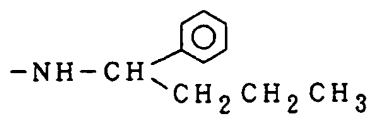
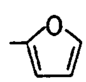
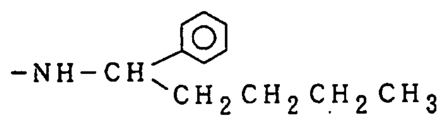
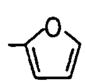
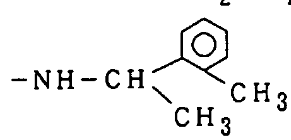
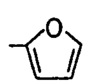
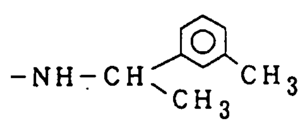
Comp. No.	A	B
211		
212		
213		$-NH-CH(CH_2CH_3)(CH_2CH_3)$
214		$-NH-CH_2C(CH_3)_3$
215		
216		
217		
218		
219		
220		

Table 1 (continued)

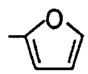
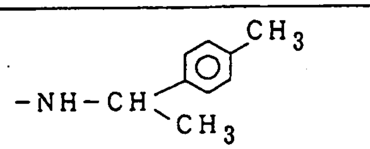
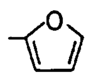
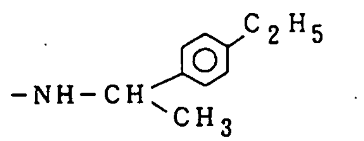
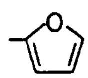
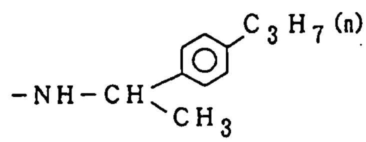
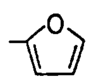
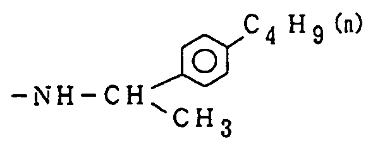
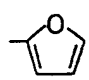
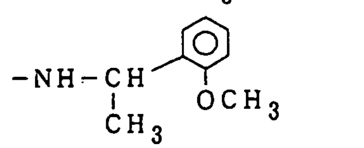
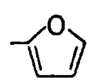
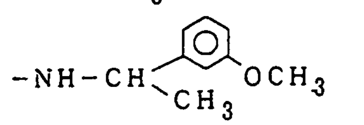
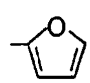
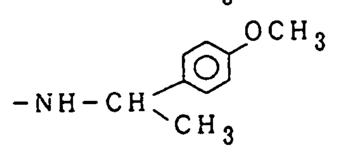
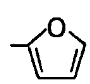
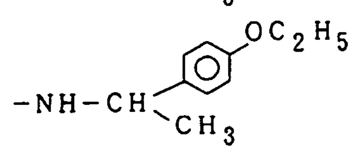
Comp. No	A	B
221		
222		
223		
224		
225		
226		
227		
228		

Table 1 (continued)

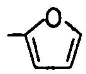
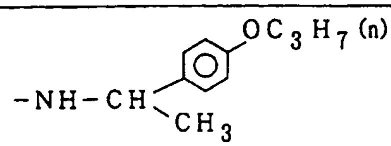
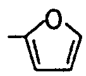
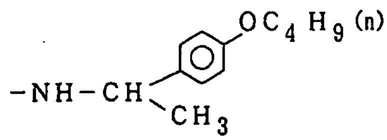
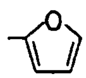
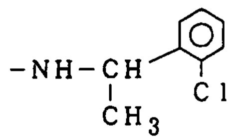
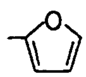
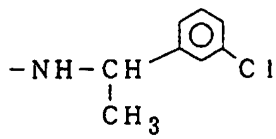
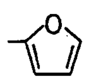
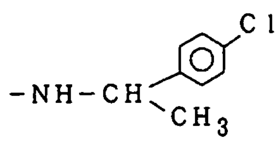
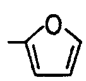
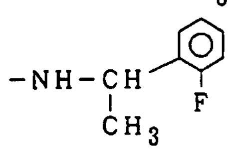
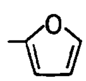
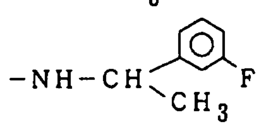
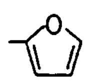
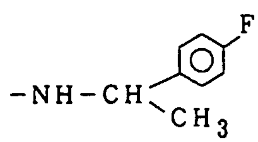
Comp. No.	A	B
229		
230		
231		
232		
233		
234		
235		
236		

Table 1 (continued)

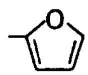
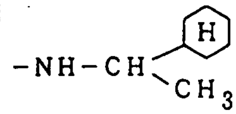
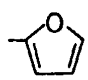
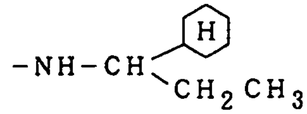
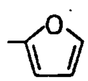
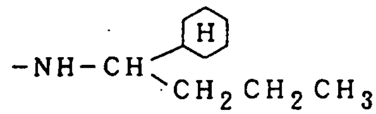
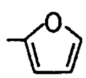
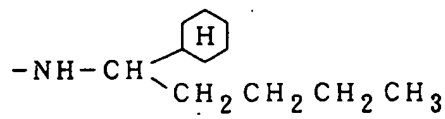
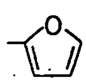
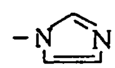
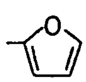
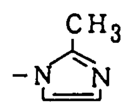
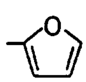
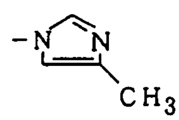
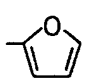
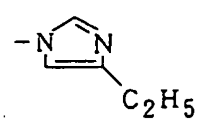
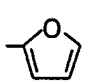
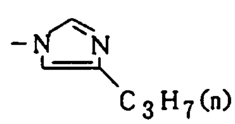
Comp. No.	A	B
237		
238		
239		
240		
241		
242		
243		
244		
245		

Table 1 (continued)

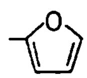
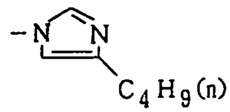
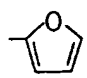
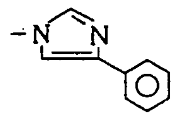
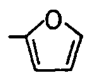
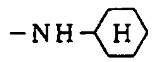
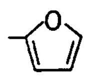
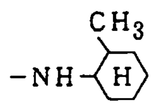
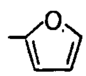
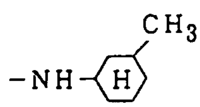
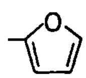
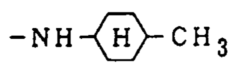
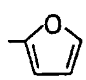
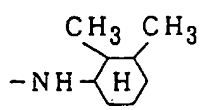
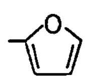
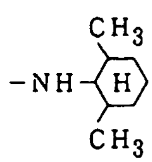
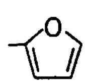
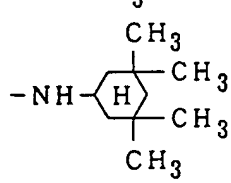
Comp. No.	A	B
246		
247		
248		
249		
250		
251		
252		
253		
254		

Table 1 (continued)

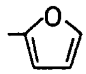
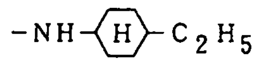
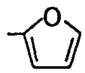
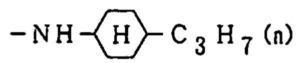
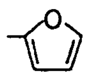
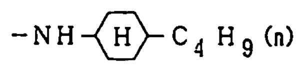
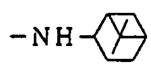
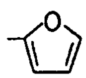
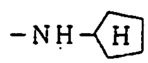
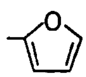
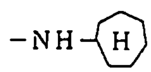
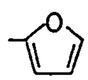
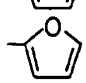
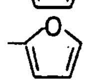
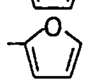
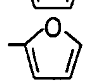
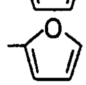
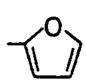
Comp. No.	A	B
255		
256		
257		
258		
259		
260		
261		$-NH-(CH_2)_2CH_3$
262		$-NH-(CH_2)_3CH_3$
263		$-NH-(CH_2)_4CH_3$
264		$-NH-(CH_2)_5CH_3$
265		$-NH-(CH_2)_6CH_3$
266		$-NH-(CH_2)_7CH_3$
267		$-NH-CH\begin{matrix}CH_2CH_3\\CH_3\end{matrix}$

Table 1 (continued)

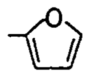
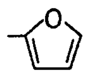
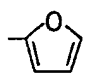
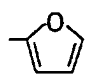
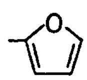
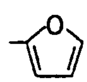
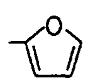
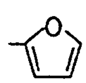
Comp. No.	A	B
268		$-NH-CH(CH_3)-(CH_2)_2CH_3$
269		$-NH-CH(CH_3)-CH(CH_3)_2$
270		$-NH-CH(CH_3)-CH_2-CH(CH_3)_2$
271		$-NH-CH(CH_3)-(CH_2)_3CH_3$
272		$-NH-CH(CH_3)-(CH_2)_4CH_3$
273		$-NH-CH(CH_3)-(CH_2)_5CH_3$
274		$-NH-CH(CH_2CH_3)-CH_2CH_3$
275		$-NH-CH(CH_2CH_3)-CH_2CH_2CH_3$
276		$-NH-CH(CH_2CH_2CH_3)-CH_2CH_2CH_3$

Table 1 (continued)

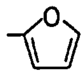
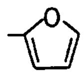
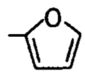
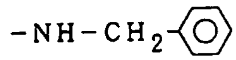
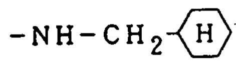
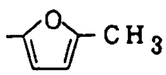
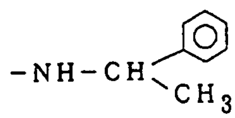
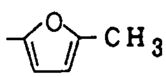
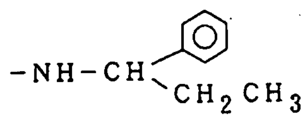
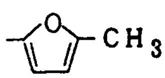
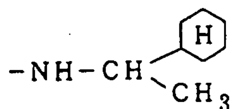
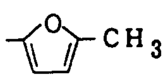
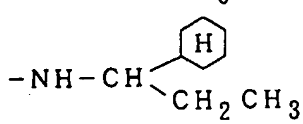
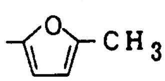
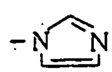
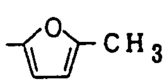
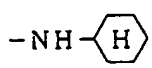
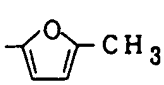
Comp. No.	A	B
277		$-NHC(CH_3)_3$
278		$-NHCH_2C(CH_3)_3$
279		
280		
281		
282		
283		
284		
285		
286		
287		$-NH-CH(CH_2CH_3)(CH_2CH_3)$

Table 1 (continued)

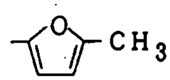
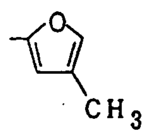
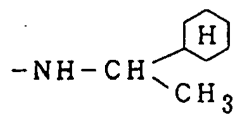
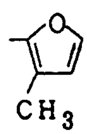
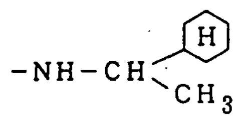
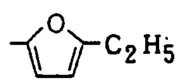
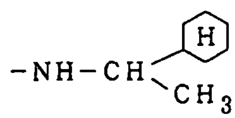
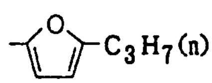
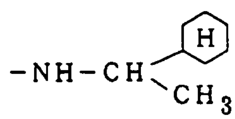
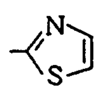
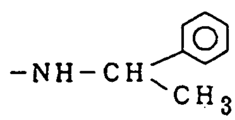
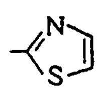
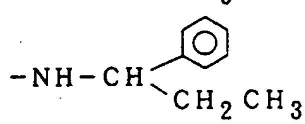
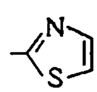
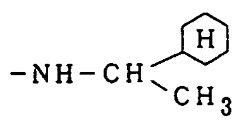
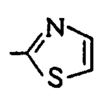
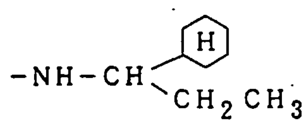
Comp. No.	A	B
288		$-NH-CH_2C(CH_3)_3$
289		
290		
291		
292		
293		
294		
295		
296		

Table 1 (continued)

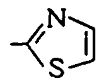
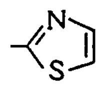
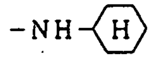
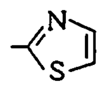
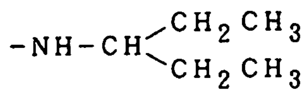
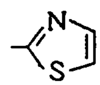
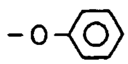
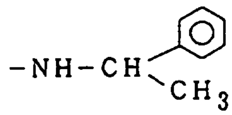
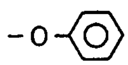
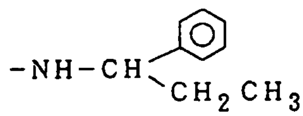
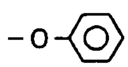
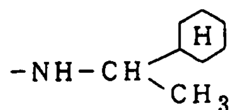
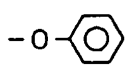
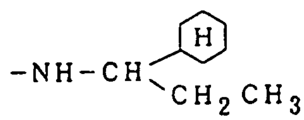
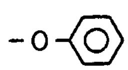
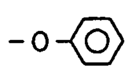
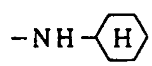
Comp. No.	A	B
297		
298		
299		
300		$-NH-CH_2C(CH_3)_3$
301		
302		
303		
304		
305		
306		

Table 1 (continued)

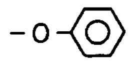
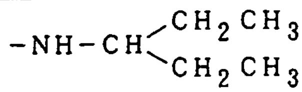
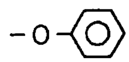
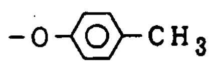
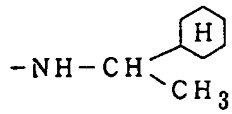
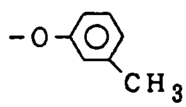
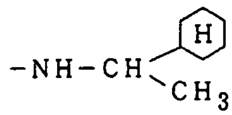
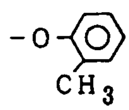
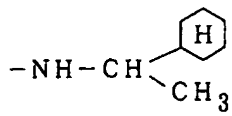
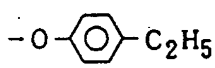
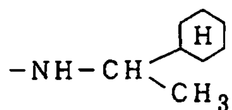
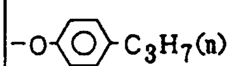
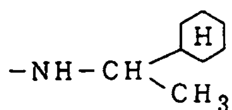
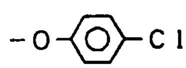
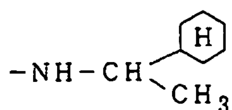
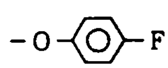
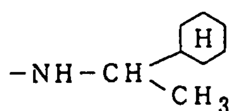
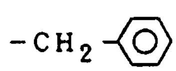
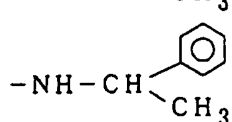
Comp. No.	A	B
307		
308		$-NH-CH_2C(CH_3)_3$
309		
310		
311		
312		
313		
314		
315		
316		

Table 1 (continued)

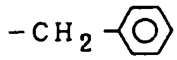
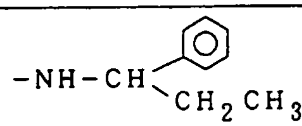
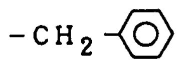
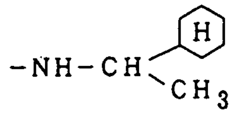
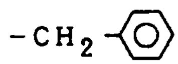
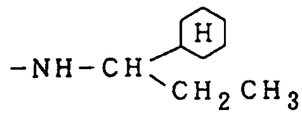
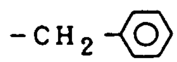
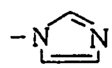
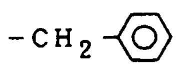
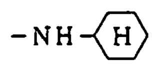
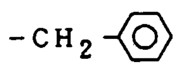
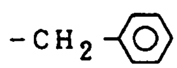
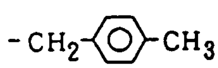
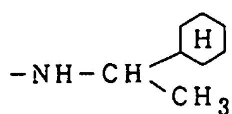
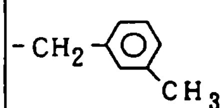
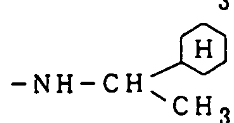
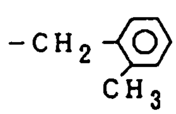
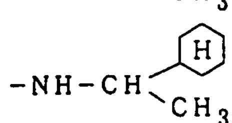
Comp. No.	A	B
317		
318		
319		
320		
321		
322		$-NH-CH(CH_2CH_3)(CH_2CH_3)$
323		$-NH-CH_2C.(CH_3)_3$
324		
325		
326		

Table 1 (continued)

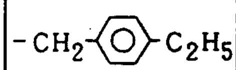
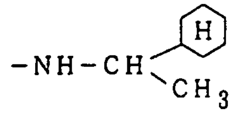
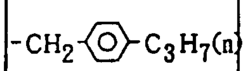
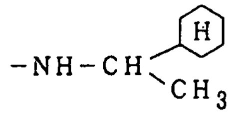
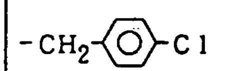
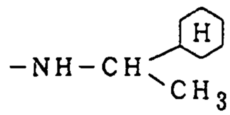
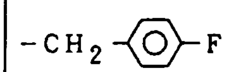
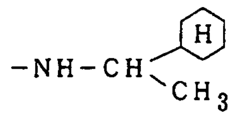
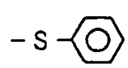
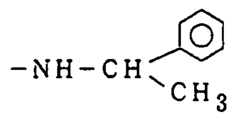
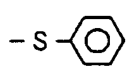
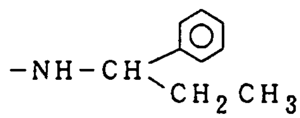
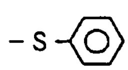
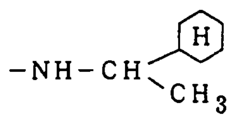
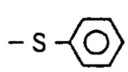
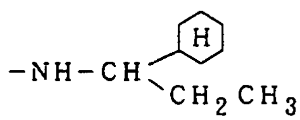
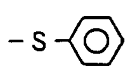
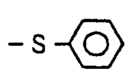
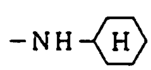
Comp. No.	A	B
327		
328		
329		
330		
331		
332		
333		
334		
335		
336		

Table 1 (continued)

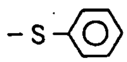
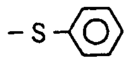
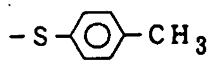
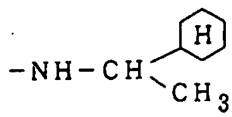
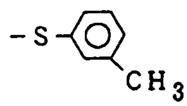
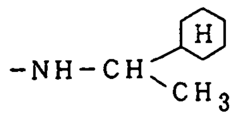
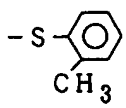
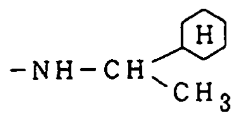
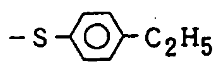
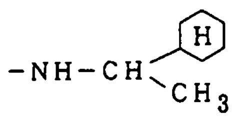
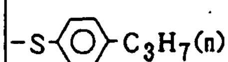
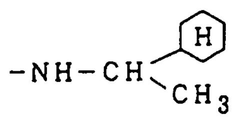
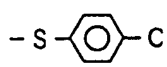
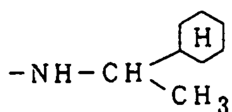
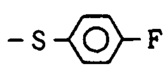
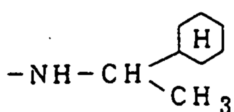
Comp. No.	A	B
337		$-NH-CH(CH_2CH_3)_2$
338		$-NH-CH_2C(CH_3)_3$
339		
340		
341		
342		
343		
344		
345		

Table 1 (continued)

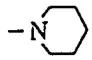
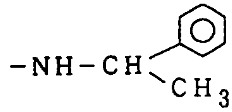
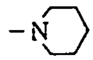
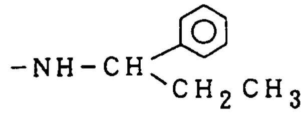
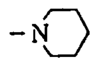
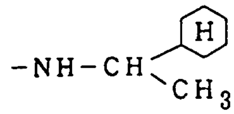
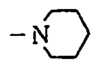
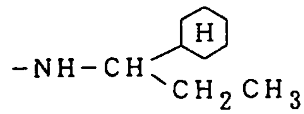
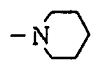
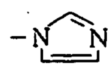
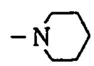
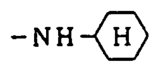
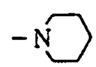
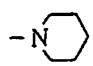
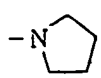
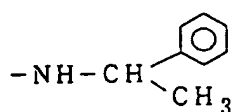
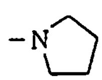
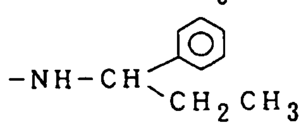
Comp. No.	A	B
346		
347		
348		
349		
350		
351		
352		$-NH-CH\begin{smallmatrix}CH_2CH_3\\CH_2CH_3\end{smallmatrix}$
353		$-NH-CH_2C(CH_3)_3$
354		
355		

Table 1 (continued)

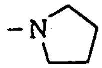
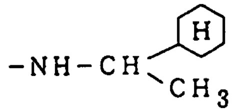
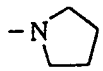
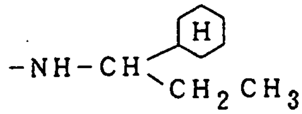
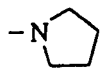
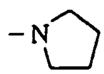
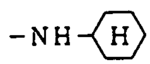
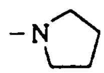
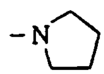
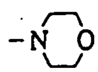
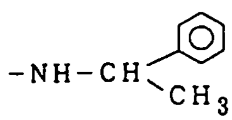
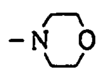
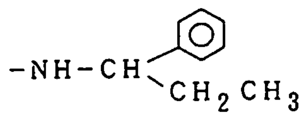
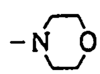
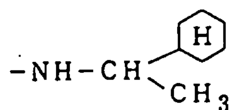
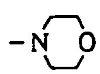
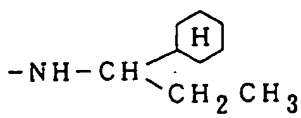
Comp. No.	A	B
356		
357		
358		
359		
360		$-NH-CH\begin{matrix}\diagup CH_2CH_3\\ \diagdown CH_2CH_3\end{matrix}$
361		$-NH-CH_2C(CH_3)_3$
362		
363		
364		
365		

Table 1 (continued)

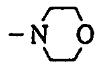
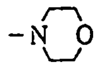
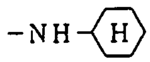
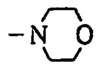
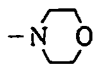
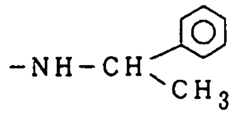
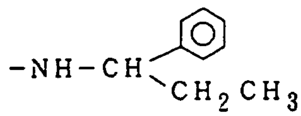
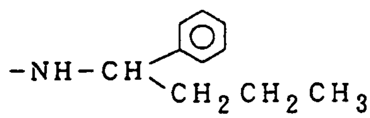
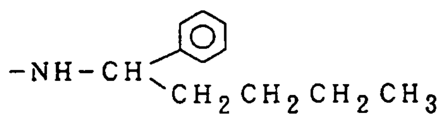
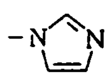
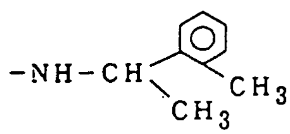
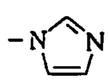
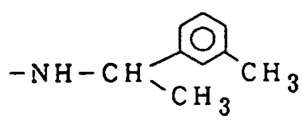
Comp. No.	A	B
366		
367		
368		$-NH-CH\begin{smallmatrix}CH_2CH_3\\CH_2CH_3\end{smallmatrix}$
369		$-NH-CH_2C(CH_3)_3$
370		
371		
372		
373		
374		
375		

Table 1 (continued)

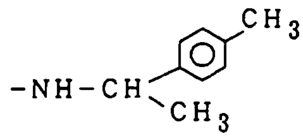
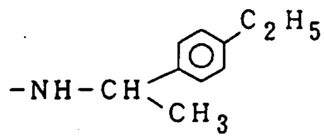
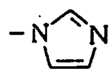
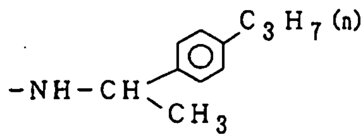
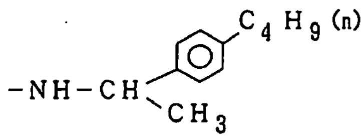
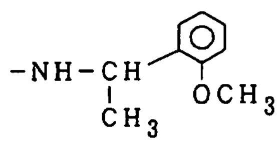
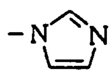
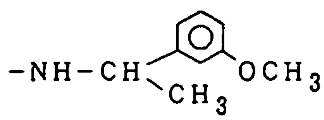
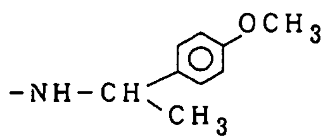
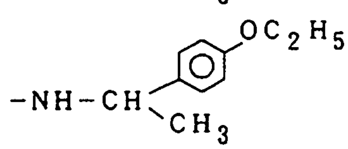
Comp. No.	A	B
376		
377		
378		
379		
380		
381		
382		
383		

Table 1 (continued)

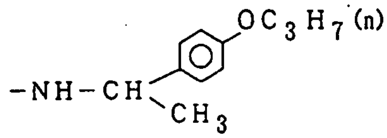
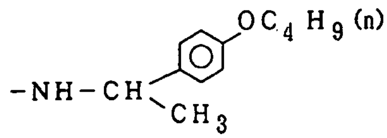
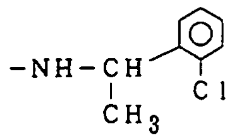
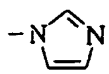
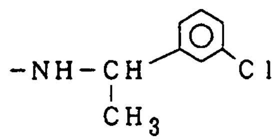
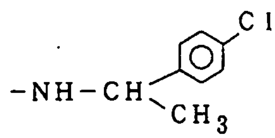
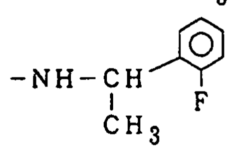
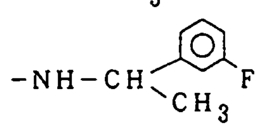
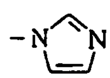
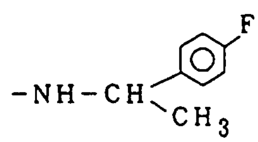
Comp. No.	A	B
384		
385		
386		
387		
388		
389		
390		
391		

Table 1 (continued)

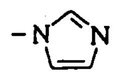
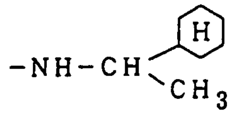
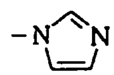
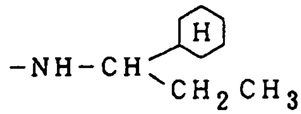
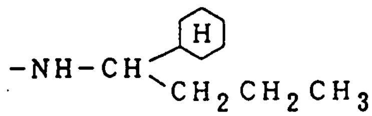
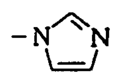
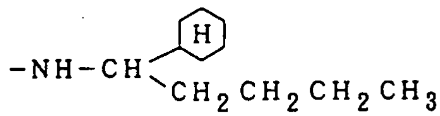
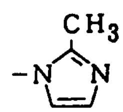
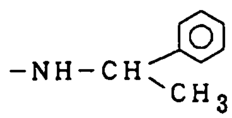
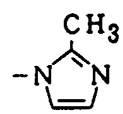
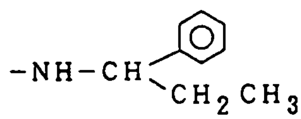
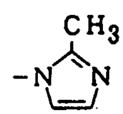
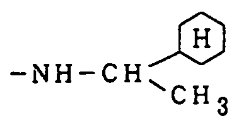
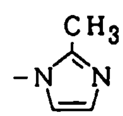
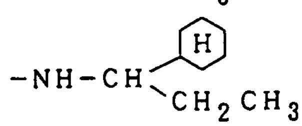
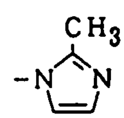
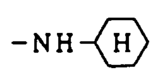
Comp. No.	A	B
392		
393		
394		
395		
396		
397		
398		
399		
400		

Table 1 (continued)

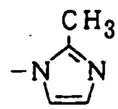
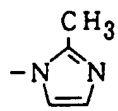
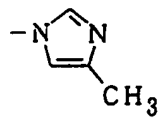
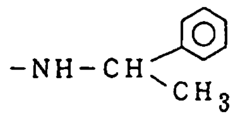
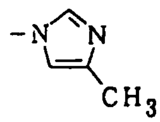
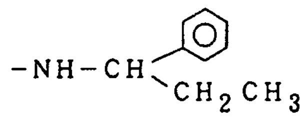
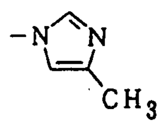
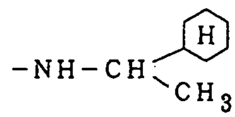
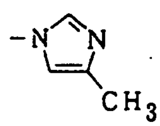
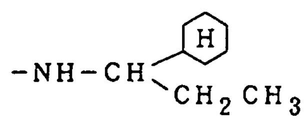
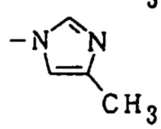
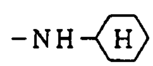
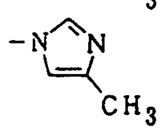
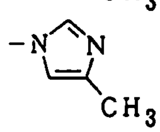
Comp. No.	A	B
401		$-NH-CH(CH_2CH_3)_2$
402		$-NH-CH_2C(CH_3)_3$
403		
404		
405		
406		
407		
408		$-NH-CH(CH_2CH_3)_2$
409		$-NH-CH_2C(CH_3)_3$

Table 1 (continued)

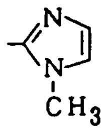
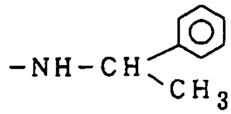
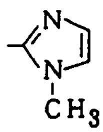
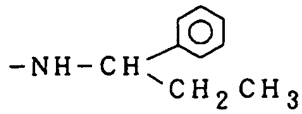
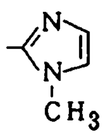
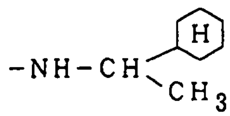
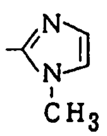
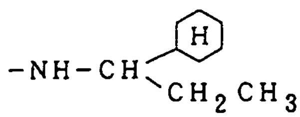
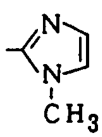
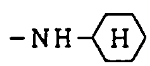
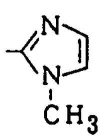
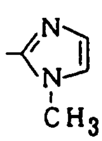
Comp. No.	A	B
410		
411		
412		
413		
414		
415		$-NH-CH(CH_2CH_3)(CH_2CH_3)$
416		$-NH-CH_2C(CH_3)_3$

Table 1 (continued)

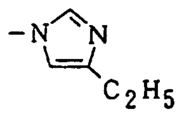
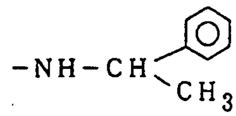
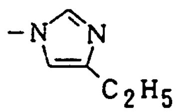
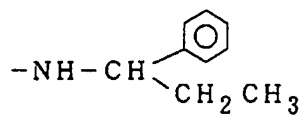
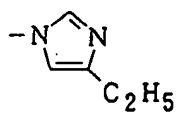
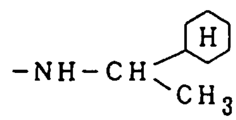
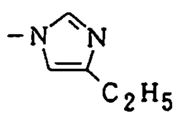
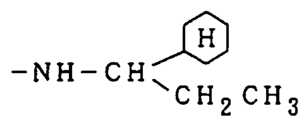
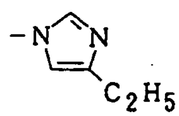
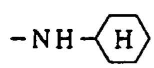
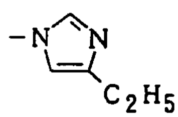
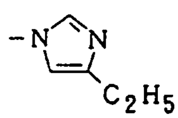
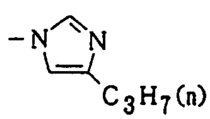
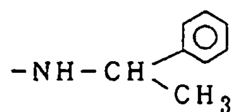
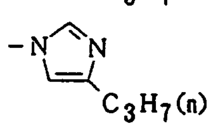
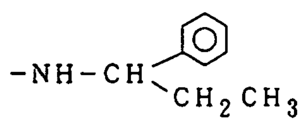
Comp. No	A	B
417		
418		
419		
420		
421		
422		$-NH-CH(CH_2CH_3)(CH_2CH_3)$
423		$-NH-CH_2C(CH_3)_3$
424		
425		

Table 1 (continued)

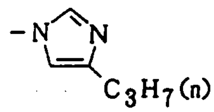
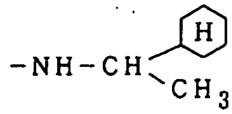
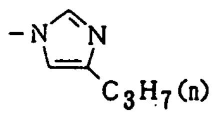
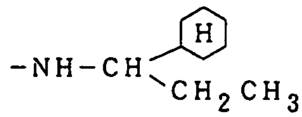
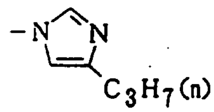
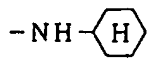
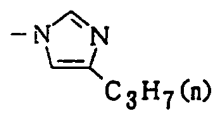
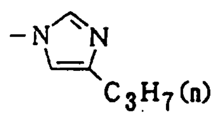
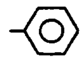
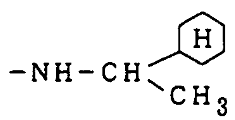
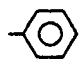
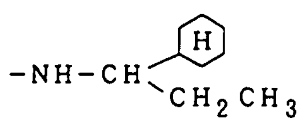
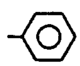
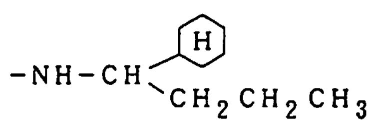
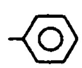
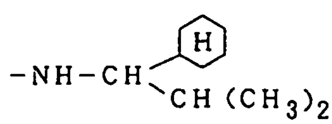
Comp. No.	A	B
426		
427		
428		
429		$-NH-CH(CH_2CH_3)_2$
430		$-NH-CH_2C(CH_3)_3$
431		
432		
433		
434		

Table 1 (continued)

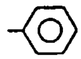
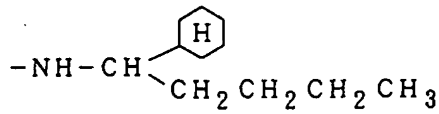
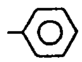
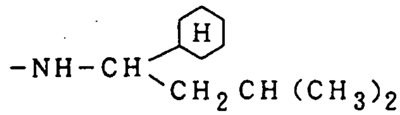
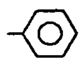
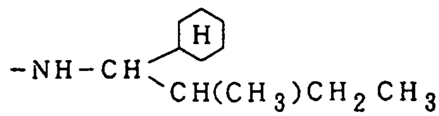
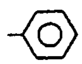
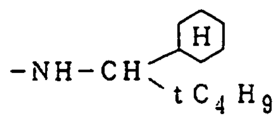
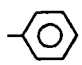
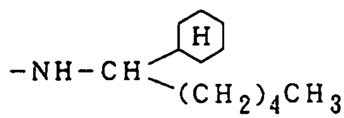
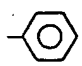
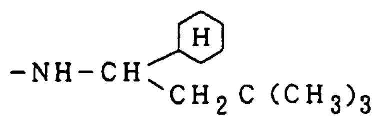
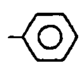
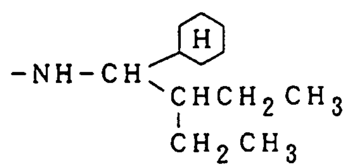
Comp. No.	A	B
435		
436		
437		
438		
439		
440		
441		

Table 1 (continued)

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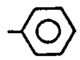
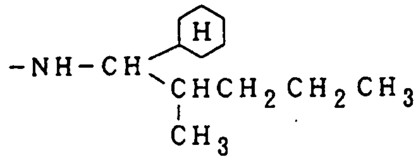
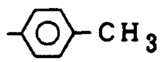
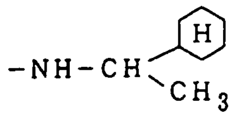
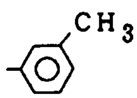
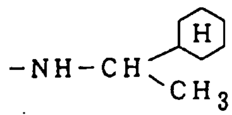
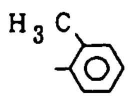
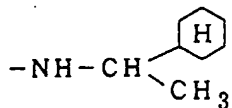
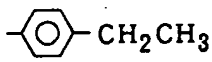
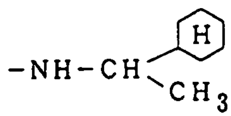
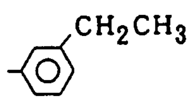
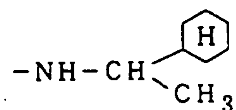
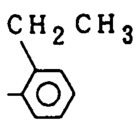
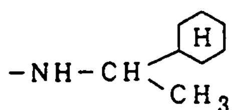
442		
443		
444		
445		
446		
447		
448		

Table 1 (continued)

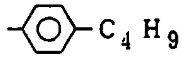
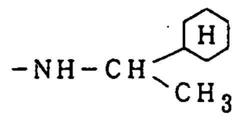
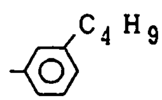
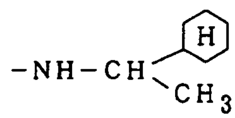
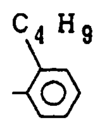
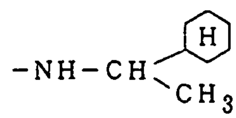
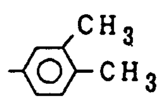
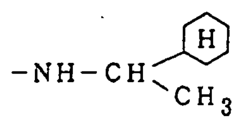
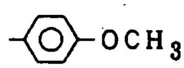
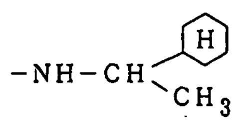
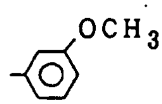
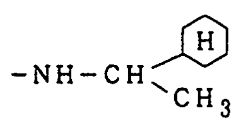
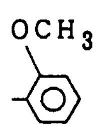
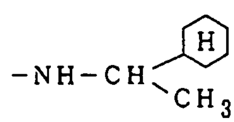
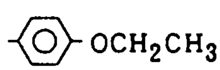
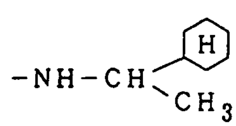
Comp. No.	A	B
449		
450		
451		
452		
453		
454		
455		
456		

Table 1 (continued)

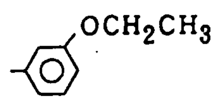
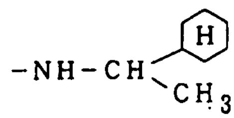
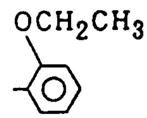
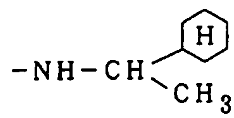
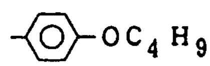
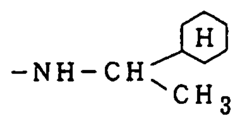
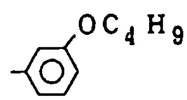
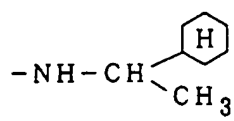
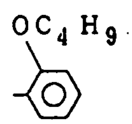
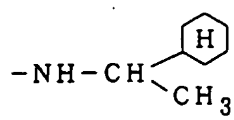
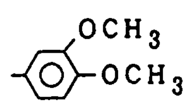
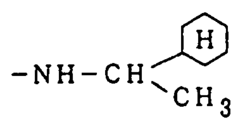
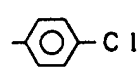
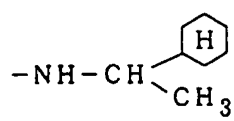
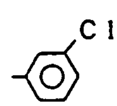
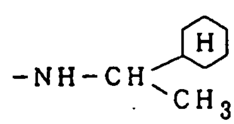
Comp. No.	A	B
457		
458		
459		
460		
461		
462		
463		
464		

Table 1 (continued)

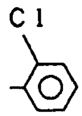
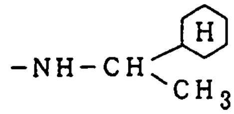
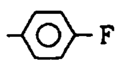
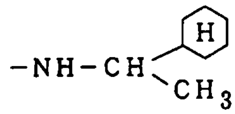
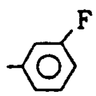
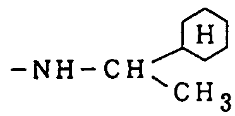
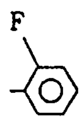
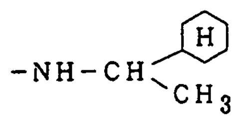
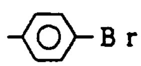
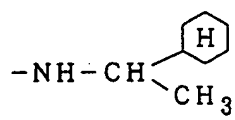
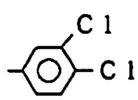
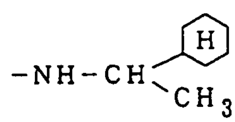
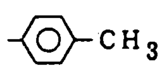
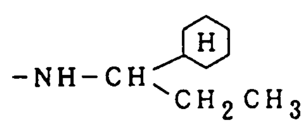
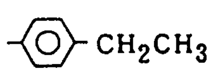
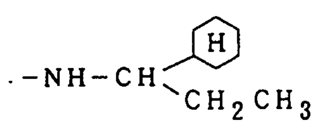
Comp. No.	A	B
465		
466		
467		
468		
469		
470		
471		
472		

Table 1 (continued)

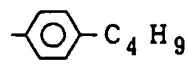
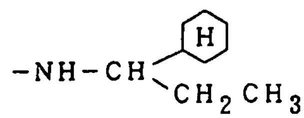
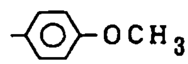
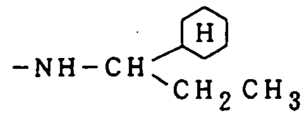
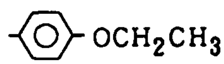
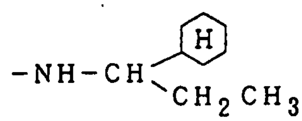
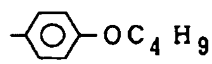
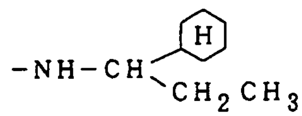
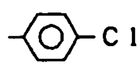
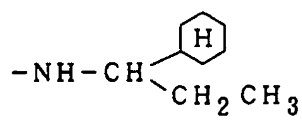
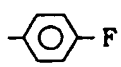
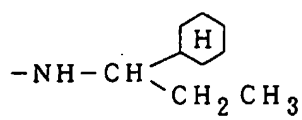
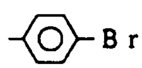
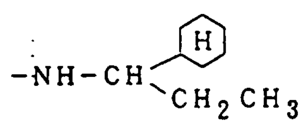
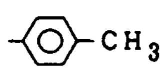
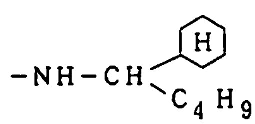
Comp. No.	A	B
473		
474		
475		
476		
477		
478		
479		
480		

Table 1 (continued)

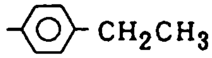
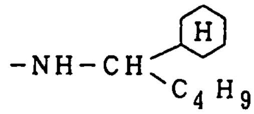
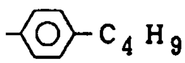
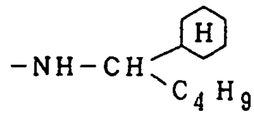
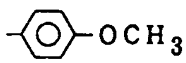
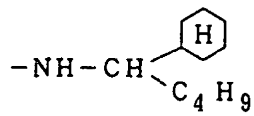
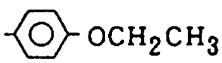
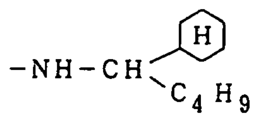
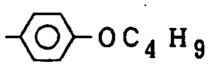
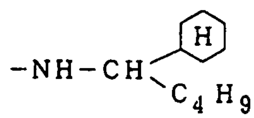
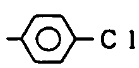
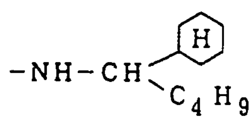
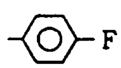
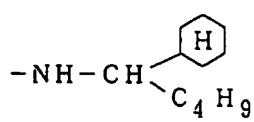
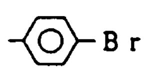
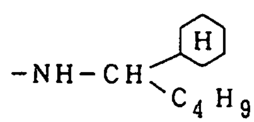
Comp. No.	A	B
481		
482		
483		
484		
485		
486		
487		
488		

Table 1 (continued)

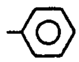
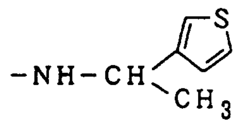
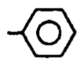
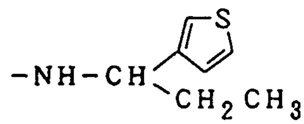
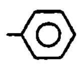
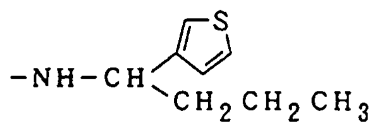
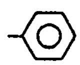
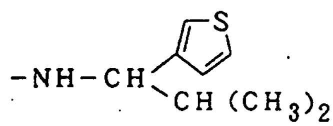
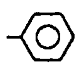
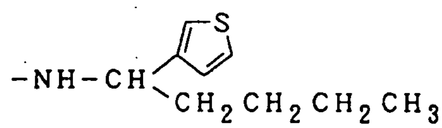
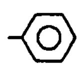
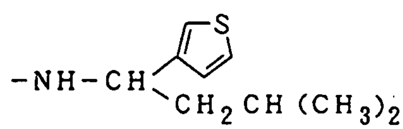
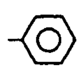
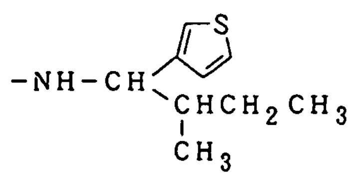
Comp. No.	A	B
489		
490		
491		
492		
493		
494		
495		

Table 1 (continued)

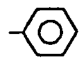
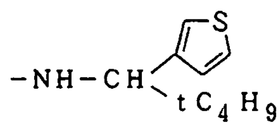
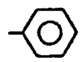
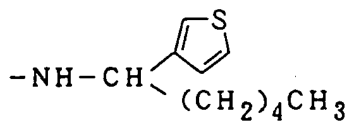
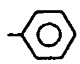
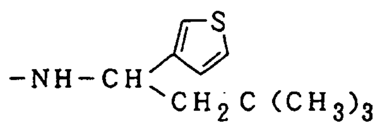
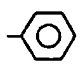
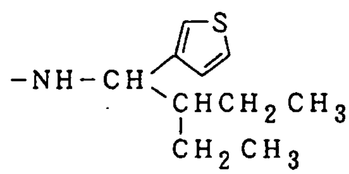
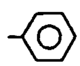
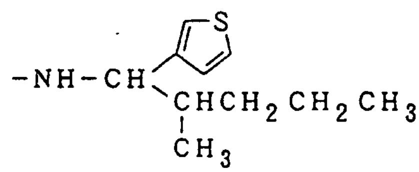
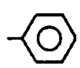
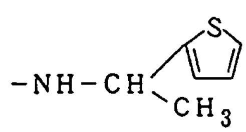
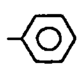
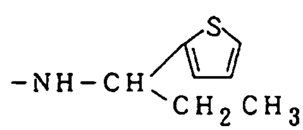
Comp. No.	A	B
496		
497		
498		
499		
500		
501		
502		

Table 1 (continued)

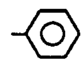
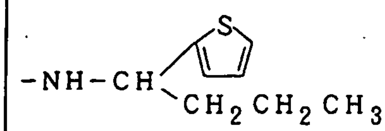
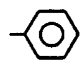
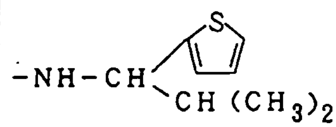
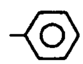
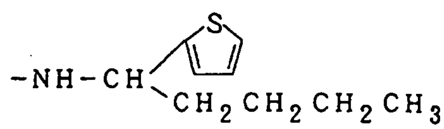
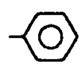
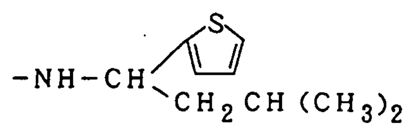
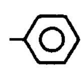
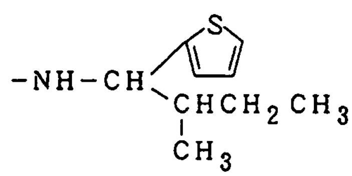
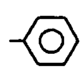
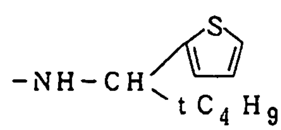
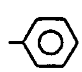
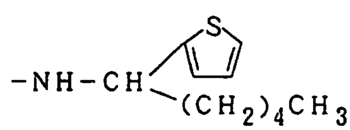
Comp. No.	A	B
503		
504		
505		
506		
507		
508		
509		

Table 1 (continued)

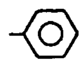
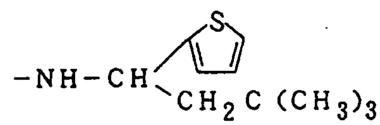
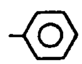
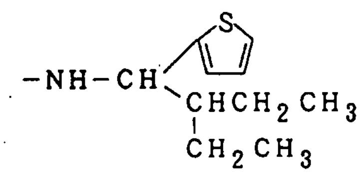
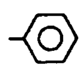
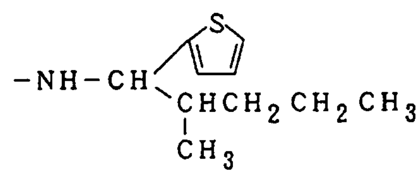
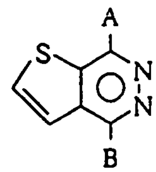
Comp. No.	A	B
510		
511		
512		

Table 2



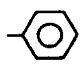
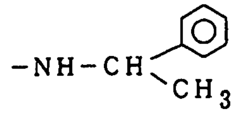
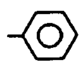
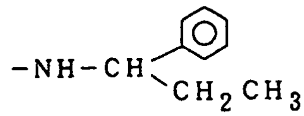
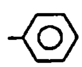
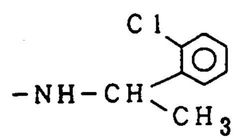
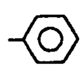
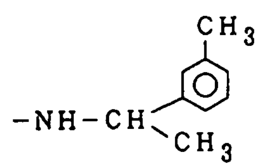
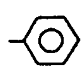
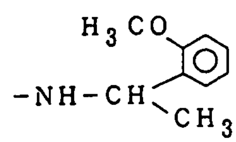
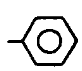
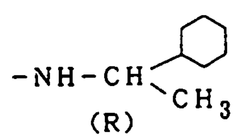
Comp. No.	A	B
513		
514		
515		
516		
517		
518		

Table 2 (continued)

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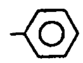
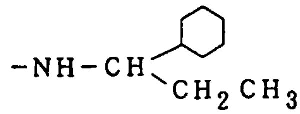
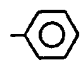
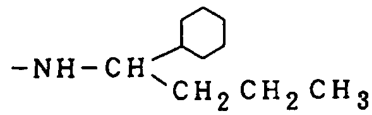
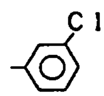
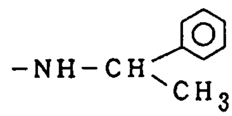
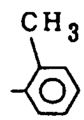
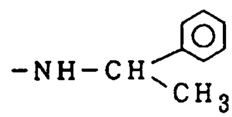
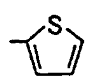
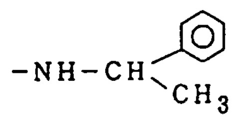
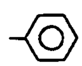
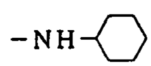
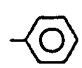
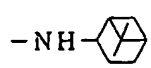
519		
520		
521		
522		
523		
524		
525		

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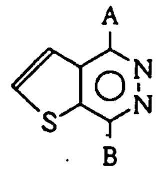


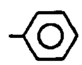
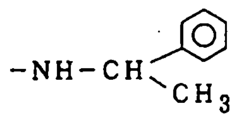
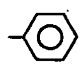
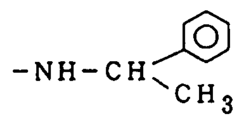
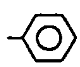
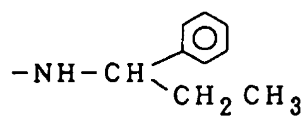
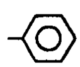
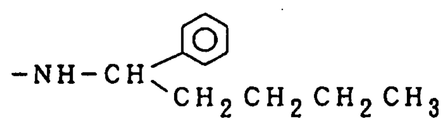
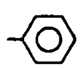
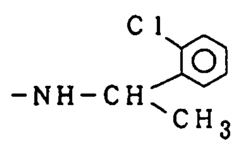
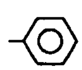
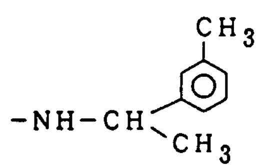
Comp. No.	A	B
526		
527		
528		
529		
530		
531		

Table 3 (continued)

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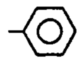
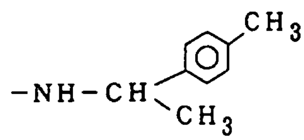
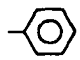
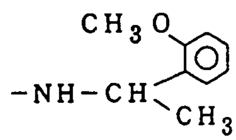
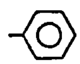
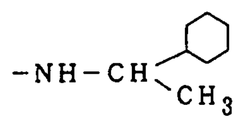
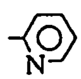
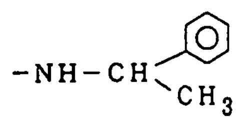
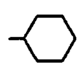
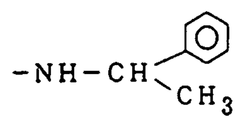
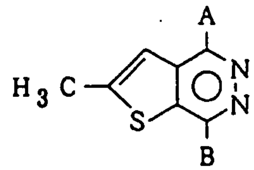
532		
533		
534		
535		
536		

Table 4



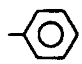
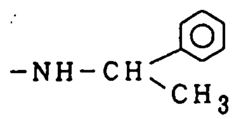
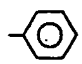
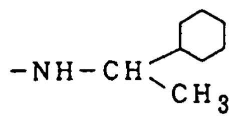
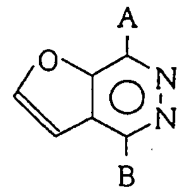
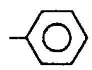
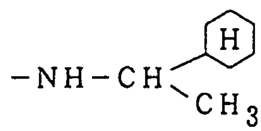
Comp. No.	A	B
537		
538		

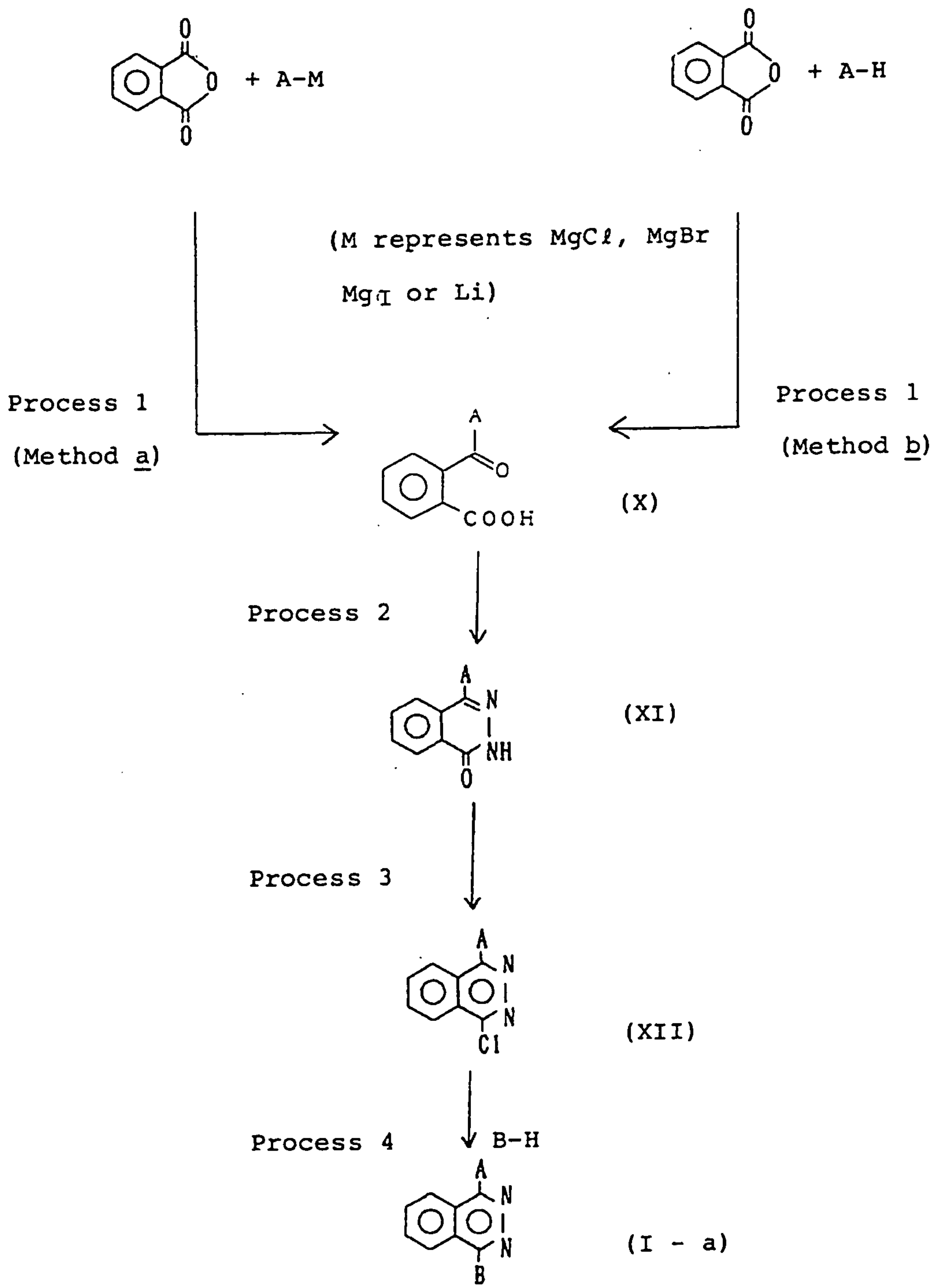
Table 5



Comp. No.	A	B
539		

A process for preparing a compound according to the present invention will now be explained. A compound according to the present invention can be synthesized by a given method which meets the object of the present invention including the following methods.

(i) When the ring C represents a benzene ring,



(A and B are as defined above)

The process 1 is a process for preparing a compound (X). The compound (X) can be prepared either by a method a or a method b. The method a is a method of preparing the compound (X) by reacting phthalic anhydride with Grignard reagent or lithium reagent. In the case of using a solvent, ether, tetrahydrofuran, dioxane, benzene, toluene, methylene chloride, dichloroethane, dimethylformamide, N-methylpyrrolidone, hexamethylphosphoroamide or the like is used either singly or in the form of a mixture. The reaction temperature is -78 to 100 °C, preferably -78 to 30 °C, and the reaction time is 10 minutes to 24 hours.

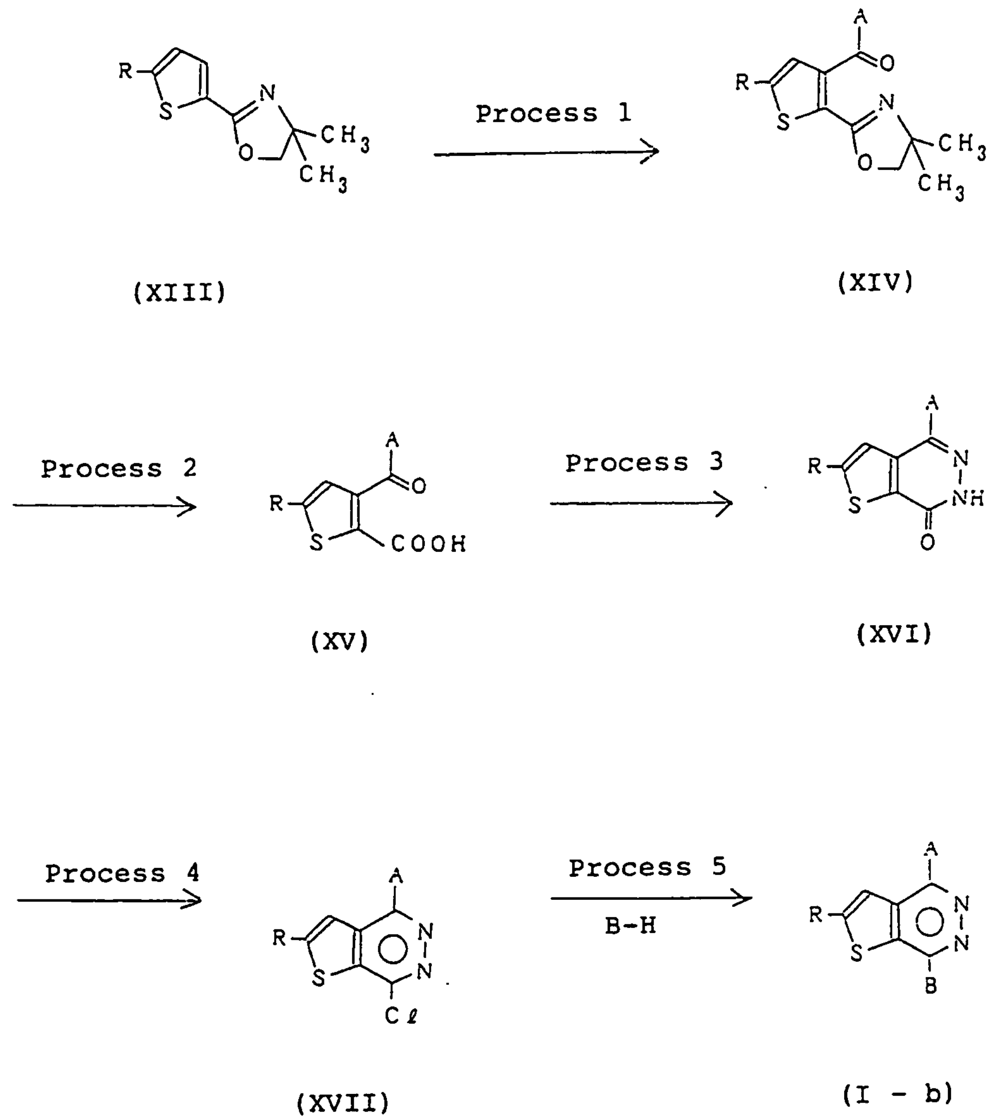
The method b is a method of preparing the compound (X) by a Friedel-Crafts reaction between phthalic anhydride and a compound represented by the formula A-H, wherein A is as defined above. In the case of using a catalyst, aluminum chloride, titanium tetrachloride, tin chloride, boron trifluoride etherate or the like is used. In the case of using a solvent, methylene chloride, dichloroethane, nitrobenzene, carbon disulfide or the like is used. The reaction temperature is -78 to 200 °C, preferably -50 to 100 °C, and the reaction time is 10 minutes to 24 hours.

The process 2 is a process for preparing a compound (XI). By reacting the compound (X) and hydrazine or hydrazine hydrate, the compound (XI) is prepared. In the case of using a solvent, water, methanol, ethanol, benzene, toluene or the like is used. The reaction temperature is 0 to 150 °C, preferably 20 to 100 °C.

The process 3 is a process for preparing a compound (XII) by a chlorination of the compound (XI) without a solvent or in a solvent such as benzene, toluene, chloroform and dichloroethane. As a chlorinating agent, thionyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride or the like is used.

The process 4 is a process for preparing a compound (I - a) according to the present invention from the compound (XII). The compound (XII) is reacted with a compound represented by the formula B-H, wherein B represents the same as defined above. Examples of solvents used are ethers such as tetrahydrofuran and dioxane; hydrocarbon halides such as chloroform and dichloroethane; aromatic hydrocarbons such as benzene, toluene, xylene and chlorobenzene; amides such as dimethylformamide and N-methylpyrrolidone; and dimethylsulfoxide. The amount of solvent used is 0.1 to 100 by weight ratio based on the compound (XII). In the case of using a catalyst, an organic base such as triethylamine, disopropylethylamine, pyridine and N,N-dimethylanyline, or an inorganic base such as NaOH, KOH, $NaHCO_3$, Na_2CO_3, $KHCO_3$ and K_2CO_3 is used. The amount of catalyst used is 0.5 to 30, preferably 1 to 10 by weight ratio based on the compound (XII). The reaction temperature is 0 to 300 °C, preferably 20 to 150 °C, and the reaction time is 10 minutes to 24 hours.

(ii) When the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms,



wherein A and B are as defined above and R represents an alkyl group having 1 to 4 carbon atoms.

The process 1 is a process for introducing

$$-\overset{\displaystyle O}{\overset{\|}{C}}-A$$

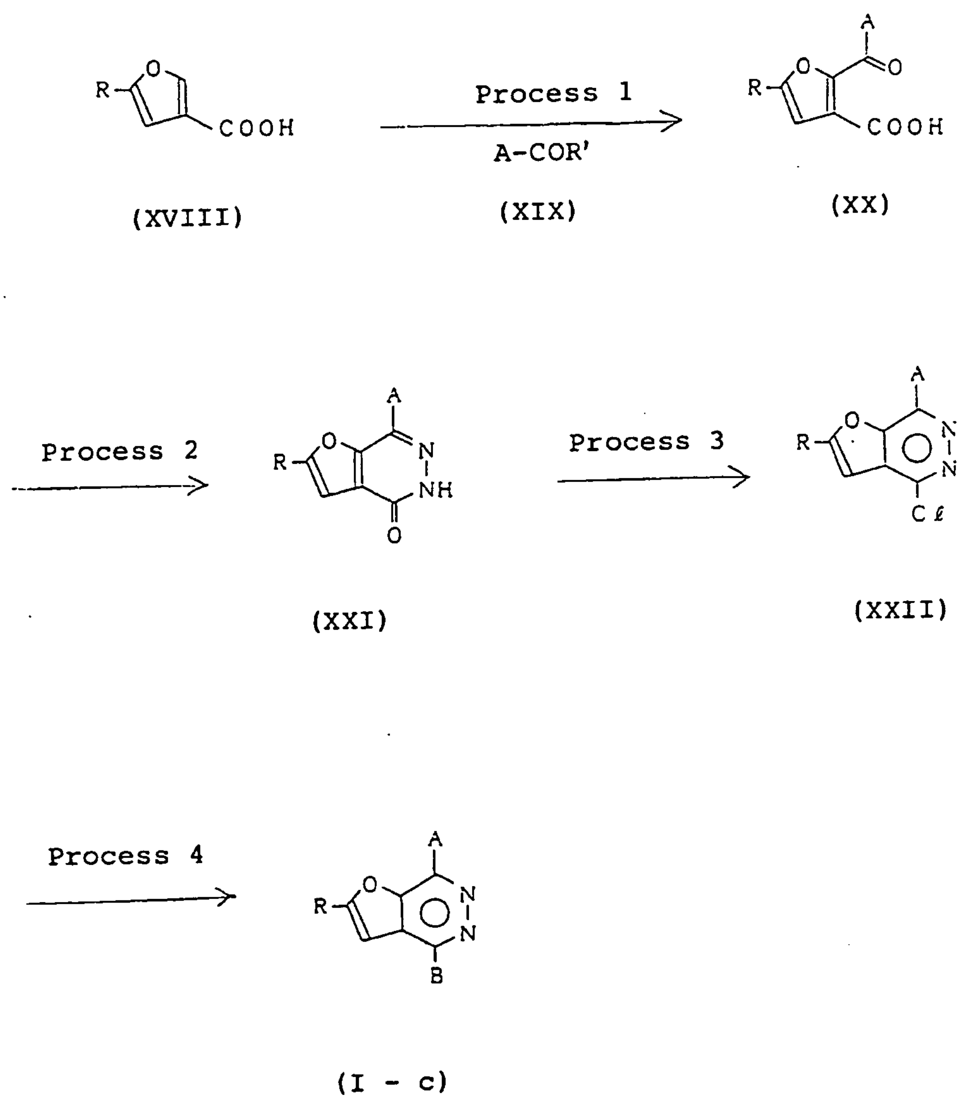
group into the ortho position of a compound (XIII) so as to prepare a compound (XIV). A base such as butyl lithium is brought into reaction with the compound (XIII) so as to produce an ortho-lithiated compound. A compound represented by the general formula A-COR' (wherein A is as defined above, and R' represents a halogen atom, an alkoxy group, an imidazolyl group or a cyano group) is then reacted with the thus-produced ortho-lithiated compound, thereby preparing the compound (XIV). In the case of using a solvent, ether, tetrahydrofuran, etc. are used either singly or in the form of a mixture.

The process 2 is a process for cleaving the oxazoline ring of the compound (XIV) so as to prepare a compound (XV). The reaction is carried out in the presence of an acid such as hydrochloric acid, sulfuric

acid, mesylic acid and tosylic acid. As a solvent, water, dioxane, tetrahydrofuran, ethanol, methanol, etc. are used either singly or in the form of a mixture.

The processes 3, 4 and 5 correspond to the processes 2, 3 and 4, respectively, in (i) when the ring C represents a benzene ring.

(iii) When the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms,



wherein A and B are as defined above and R represents an alkyl group having 1 to 4 carbon atoms.

The process 1 is a process for introducing A-C=O group into the second position of a compound (XVIII) so as to prepare a compound (XX). The reaction is carried out by bringing the dilithiated compound of the compound (XVIII) which is produced by a base into reaction with a compound represented by the general formula A-COR' (wherein A is as defined above, and R'represents a halogen atom, an alkoxy group, an aryloxy group, an imidazolyl group or a cyano group). At this time, n-butyllithium, s-butyllithium, LDA, LHMDS, etc. are usable as a base. The amount of base used is 1 to 10, preferably 2 to 4 by molar ratio. As a solvent, tetrahydrofuran, diethyl ether, diisopropyl ether, hexane, heptane, etc. are used either singly or in the form of a mixture.

The processes 2, 3, and 4 correspond to the processes 2, 3 and 4, respectively, in (i) when the ring C represents a benzene ring.

The salts of the compound represented by the general formula (I) are preferably physiologically tolerable salts. They are, for example, the salts of inorganic acids such as hydrochlorides, hydrobromides, hydroiodides, sulfides and phosphates, and the salts of organic acids such as methane sulfonates, p-toluene sulfonates, benzene sulfonates, camphor sulfonates, acetates, benzoates, malates, lactates, glycolates, glucronates, maleates, fumarates, oxalates, ascorbates, citrates, salicylates, nicotinates and tartrates. Since some compounds represented by the general formula (I) and some salts thereof exist in the form of a hydrate or a solvate, the compounds of the present invention include the hydrates and solvates thereof.

When a compound of the present invention is orally administered to an adult as a medicine, it is preferable that a dose of 1 to 100 mg is administered 1 to 3 times a day. In the case of using a compound of the present invention as an intravenous injection for an adult, it is preferable that a dose of 0.01 to 10 mg is administered 2 to 5 times a day. In the case of using a compound of the present invention as a medicine for intestinal administration for an adult, it is preferable that a dose of 1 to 100 mg is administered 1 to 3 times a day. It is more preferable to appropriately increase or decrease the dose depending upon the age, the condition of the disease and the condition of the patient.

When a compound of the present invention is formed into a medicine, at least one compound represented by the general formula (I) or at least one pharmaceutically tolerable salt thereof is mixed with a pharmaceutical carrier, a shaping agent and other additives. The carrier may be either a solid or a liquid. Examples of a solid carrier are lactose, white clay (kaolin), sucrose, crystalline cellulose, cornstarch, talc, agar agar, pectin, acacia gum, stearic acid, magnesium stearate, lecithin and sodium chloride.

Examples of a liquid carrier are syrup, glycerin, peanut oil, polyvinyl pyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, and water.

Such a medicine may be used in various forms. In the case of using a solid carrier, a medicine may be prepared in the form of tablets, powder, hard gelatin capsules, suppositories or troche. The amount of solid carrier may be varied in a wide range, but it is preferably about 1 mg to 1 g.

In the case of using a liquid carrier, a medicine may be prepared in the form of syrup, emulsion, soft gelatin capsule, sterile injection contained in an ampule or the like, or aqueous or nonaqueous suspension.

The present invention will be explained in more detail hereinunder with reference to the following examples. It is however, to be understood that the present invention is not restricted thereto and any modification is possible within the scope of the present invention.

[Examples]

Example 1

Synthesis of (R)-1-(α-phenylethylamino)-4-cyclohexylphthalazine (Compound No. 1 in Table 1)

10.0 g of phthalic anhydride was dissolved in 200 mℓ of tetrahydrofuran, and 40 mℓ of cyclohexylmagnesium chloride (2.0 M, ether solution) was added dropwise to the solution at -50 °C. After stirring the solution at the same temperature for 1 hour, the reaction solution was poured into 0.5-N hydrochloric acid, and extracted with chloroform. After the organic layer was dried over magnesium sulfide, it was purified by silica gel chromatography (eluent: chloroform-methanol) to obtain 12.0 g of o-(cyclohexanoyl) benzoic acid.

12.0 g of o-(cyclohexanoyl) benzoic acid and 3.1 g of hydrazine hydrate were dissolved in 60 mℓ of ethanol, and the solution was refluxed for 4 hours. Ethanol was distilled off and the remaining solution was crystallized by adding ether, thereby obtaining 7.5 g of 4-cyclohexyl-1-phthalazinone.

1.0 g of 4-cyclohexyl-1-phthalazinone and 5 mℓ of phosphorus oxychloride were dissolved in 10 mℓ of dichloroethane, and the solution was stirred at 100 °C for 4 hours. The reaction solution was distilled off, and a 1-N aqueous NaOH solution was added thereto under cooling with ice. The solution was extracted with chloroform and dried over magnesium sulfide. The solvent was then distilled off, thereby obtaining 1.1g of 1-chloro-4-cyclo-hexylphthalazine.

1.1g of 1-chloro-4-cyclohexylphthalazine and 1.6 g of D-α-phenylethylamine were dissolved in N-methylpyrrolidone, and the solution was stirred at 140 °C for 6 hours. After cooling the solution, an aqueous 5% NaOH solution was added to the solution, and the resultant solution was extracted with chloroform. The organic layer was dried, concentrated, purified by silica gel chromatography (eluent: hexane, chloroform, ethyl acetate), and recrystallized from ether to obtain 1.05 g of (R)-1-(α-phenylethylamino)-4-cyclohexylphthalazine.

Melting point: 162.5 to 164.0 °C.

Examples 2 to 38

Compounds of Examples 2 to 38 shown in Table 6 were synthesized in accordance with the method in Example 1.

Example 39

Synthesis of (R)-1-(α-phenylethylamino)-4-(3-thienyl) phthalazine (Compound No. 207 in Table 1)

35 mℓ of normal butyllithium (1.5 M, hexane solution) was dissolved in 50 mℓ of ether, and 6.0 g of 3-bromthiophene was added dropwise to the solution at -70°C. Separately from this, 5.5 g of phthalic anhydride was dissolved in 80 mℓ of tetrahydrofuran, and the lithium reagent obtained above wad added dropwise to this solution at -70°C.

After stirring the solution at the same temperature for 1 hour, the reaction solution was poured into 0.5-N hydrochloric acid, and extracted with chloroform. After the organic layer was dried over magnesium sulfide, it was purified by silica gel chromatography (eluent: chloroform-methanol) to obtain 1.8 g of o-(3-thenoyl)benzoic acid.

1.8 g of o-(3-thenoyl)benzoic acid and 580 mg of hydrazine hydrate were dissolved in 20 mℓ of ethanol, and the solution was refluxed for 4 hours. After cooling the solution, it was crystallized by adding ether, thereby obtaining 910 mg of 4-(3-thienyl)-1-phthalazinone

500 mg of 4-(3-thienyl)-1-phthalazinone and 3 mℓ of phosphorus oxychloride were dissolved in 6 mℓ of dichloroethane, and the solution was stirred at 100°C for 4 hours. The reaction solution was distilled off, and a 1-N aqueous NaOH solution was added thereto under cooling with ice. The solution was extracted with chloroform and dried over magnesium sulfide. The solvent was then distilled off, thereby obtaining 515 mg of 1-chloro-4-(3-thienyl)phthalazine.

510 mg of 1-chloro-4-(3-thienyl)phthalazine and 790 mg of D-α-phenylethylamine were dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 140°C for 6 hours. After cooling the solution, an aqueous 5% NaOH solution was added to the solution, and the resultant solution was extracted with chloroform. The organic layer was dried, concentrated, purified by silica gel chromatography (eluent: hexane, chloroform, ethyl acetate), and recrystallized from ether to obtain 492 mg of (R)-1-(α-phenylethylamino)-4-(3-thienyl)phthalazine.

Melting point: 144.0 to 146.0°C.

Examples 40 and 41

Compounds of Examples 40 and 41 shown in Table 6 were synthesized in accordance with the method in Example 39.

Example 42

Synthesis of (R)-1-(α-phenylethylamino)-4-(4-methyl-2-thienyl)phthalazine (Compound No. 189 in Table 1)

1.90 g of phthalic anhydride and 3.58 g of aluminum chloride were dissolved in 40 mℓ of dichloroethane, and 2-bromo-3-methylthiophene was added dropwise to the solution at room temperature. After stirring the solution for 4 hours, the reaction solution was poured into a 1-N hydrochloric acid under cooling with ice, and extracted with chloroform. By purifying the extract by silica gel chromatography (eluent: chloroform, ethyl acetate), 1.70 g of o-(5-bromo-2-thenoyl)benzoic acid was obtained.

1.70 g of o-(5-bromo-2-thenoyl)benzoic acid and hydrazine hydrate were dissolved in 40 mℓ of ethanol, and the solution was refluxed for 4 hours. After cooling the solution, it was crystallized by adding ether, thereby obtaining 315 mg of 4-(5-bromo-4-methyl-2-thienyl)-1-phthalazinone.

300 mg of 4-(5-bromo-4-methyl-2-thienyl)-1-phthalazinone, 500 mg of 5% palladium carbon (Pd-C) and 1 mℓ of concentrated hydrochloric acid were added to 50 mℓ of ethanol, and hydrogen gas was reacted with the resulting mixture under ordinary pressure. After the end of the reaction, the mixture was filtered, and the filtrate was concentrated to obtain 205 mg of 4-(4-methyl-2-thienyl)phthalazinone.

200 mg of 4-(4-methyl-2-thienyl)phthalazinone and 2 mℓ of phosphorus oxychloride were dissolved in 4 mℓ of dichloroethane, and the solution was stirred at 100°C for 4 hours. The reaction solution was distilled off, and a 1-N aqueous NaOH solution was added thereto under cooling with ice. The solution was extracted with chloroform, dried and concentrated to obtain 206 mg of 1-chloro-4-(4-methyl-2-thienyl)phthalazine.

200 mg of 1-chloro-4-(4-methyl-2-thienyl)phthalazine and 100 mg of D-α-phenylethylamine were dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 140° C for 8 hours. After the solution was subjected to aftertreatment, it was purified by column chromatography, thereby obtaining 25 mg of (R)-1-(α-phenylethylamino)-4-(4-methyl-2-thienyl) phthalazine.

Melting point: 118.5 to 121. 0° C.

Examples 43 and 44

Compounds of Examples 43 and 44 shown in Table 6 were synthesized in accordance with the method in Example 42.

Example 45

Synthesis of (R)-1-(α-cyclohexylethylamino)-4-(2-furyl) phthalazine (Compound No. 237 in Table 1)

3.4 g of furan was dissolved in 30 mℓ of tetrahydrofuran, and the solution was added dropwise to 34 mℓ of normal butyllithium (1.6 M, hexane solution) at -40° C. After stirring the resultant solution at 0° C for 4 hours, the lithium reagent was added dropwise to a solution of 7.4 g of phthalic anhydride in 100 mℓ of tetrahydrofuran at -70° C. After stirring the solution at the same temperature for 1 hour, the reaction solution was poured into 0.5-N hydrochloric acid, and extracted with chloroform. By purification by column chromatography (eluent: chloroform, methanol), 2.0 g of o-(2-furoyl) benzoic acid was obtained.

2.0 g of o-(2-furoyl) benzoic acid and 690 mg of hydrazine hydrate were dissolved in 30 mℓ of ethanol, and the solution was refluxed for 4 hours.

After cooling the solution, it was crystallized by adding ether, thereby obtaining 1.0 g of 4-(2-furyl)-1-phthalazinone.

1.0 g of 4-(2-furyl)-1-phthalazinone and 5 mℓ of phosphorus oxychloride were dissolved in 5 mℓ of dichloroethane, and the solution was stirred at 100° C for 3 hours. The reaction solution was distilled off, and a 1-N aqueous NaOH solution was added thereto under cooling with ice. The solution was extracted with chloroform, dried and concentrated to obtain 910 mg of 1-chloro-4-(2-furyl))phthalazine.

300 mg of 1-chloro-4-(2-furyl)phthalazine and 495 mg of R-cyclohexylethylamine were dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 150° C for 8 hours. After the solution was subjected to after-treatment, it was purified by column chromatography, thereby obtaining 135 mg of (R)-1-(α-cyclohexylethylamino)-4-(3-furyl) phthalazine.

Melting point: 152.0 to 153.0° C.

Example 46

Synthesis of 1-(1-imidazolyl)-4-(2-furyl)phthalazine (Compound No. 241 in Table 1)

300 mg of 1-chloro-4-(2-furyl)phthalazine and 707 mg of imidazol were dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 150° C for 10 hours. After the solution was subjected to after-treatment, it was purified by column chromatography, thereby obtaining 14.5 mg of 1-(1-imidazolyl)-4-(2-furyl)phthalazine.

Melting point: 151.0 to 152.5° C.

Examples 47 to 59

Compounds of Examples 47 to 59 and 59' shown in Table 6 were synthesized in accordance with the method in Example 46.

Example 60

Synthesis of (R)-1-(1-cyclohexylethylamino)-4-phenylphthalazine (R compound of Compound No. 431 in Table 1)

722 mg (3.0 mmol) of 1-chloro-4-phenylphthalazine and 1.15 g (9.0 mmol) of (R)-(-)-1-cyclohexylethylamine were added to 2 mℓ of N–methylpyrrolidone, and the resultant mixture was stirred at 120 to 130° C for 6 hours under heating. After the end of the reaction, the mixture was cooled. 20 mℓ of an

aqueous 5% NaOH solution was added to the mixture and the solution was extracted with chloroform. The organic layer was dried over $MgSO_4$, concentrated, purified by silica gel chromatography (eluent: ethyl acetate : hexane : chloroform = 1 : 3 : 1) and recrystallized from ether-chloroform, thereby obtaining 751 mg of (R)-1-(1-cyclohexylethylamino)-4-phenylphthalazine.

Melting point: 164.0 to 167.0°C.

Examples 61 to 68

Compounds of Examples 61 to 68 shown in Table 6 were synthesized in accordance with the method in Example 60.

Table 6

Comp. of Ex. No. (Comp. No. in Table1)	m. p. (℃)
2 (No. 2)	178.5～180.0
3 (No. 34)	182.0～184.0
4 (No. 44)	172.0～174.5
5 (No. 40)	221.5～222.0
6 (No. 58)	amorphous
7 (No. 23)	amorphous
8 (No. 27)	165.0～170.0
9 (No. 67)	121.0～122.0
10 (No. 75)	125.0～125.5
11 (No. 91)	178.0～179.0
12 (No. 316)	amorphous
13 (No. 329)	amorphous
14 (No. 301)	181.0～184.0
15 (No. 331)	152.0～153.5
16 (No. 161)	amorphous
17 (No. 162)	107.0～109.0
18 (No. 167)	125.0～130.0
19 (No. 177)	177.0～180.0
20 (No. 178)	188.0～189.0
21 (No. 168)	amorphous
22 (No. 174)	139.0～145.0
23 (No. 169)	109.0～110.5
24 (No. 170)	132.5～135.5
25 (No. 173)	oil
26 (No. 150)	amorphous
27 (No. 152)	amorphous
28 (No. 115)	140.0～141.0

Comp. of Ex. No. (Comp. No. in Table1)	m. p. (℃)
29 (No. 116)	139.5～143.0
30 (No. 118)	133.0～135.0
31 (No. 120)	119.0～121.5
32 (No. 131)	198.5～201.0
33 (No. 125)	164.0～165.0
34 (No. 137)	88.0～92.0
35 (No. 138)	amorphous
36 (No. 141)	162.0～163.5
37 (No. 142)	154.0～155.0
38 (No. 147)	194.0～195.5
40 (No. 208)	152.0～156.0
41 (No. 181)	178.0～179.5
43 (No. 197)	134.0～136.5
44 (No. 215)	149.0～152.5
47 (No. 354)	130.0～134.0
48 (No. 346)	168.0～171.0
49 (No. 362)	160.0～161.0
50 (No. 370)	170.0～174.0
51 (No. 371)	199.5～201.0
52 (No. 373)	183.0～185.5
53 (No. 375)	192.0～193.5
54 (No. 386)	195.0～197.0
55 (No. 380)	151.0～152.5
56 (No. 396)	110.0～116.0
57 (No. 403)	85.0～90.0
58 (No. 410)	118.0～119.0
59 (No. 293)	135.0～136.5
59′ (No. 283)	168 ～175 decomposition

Table 6 (continued)

Comp. of Ex. No. (Comp. No. in Table1)	m. p. (℃)	Comp. of Ex. No. (Comp. No. in Table1	m. p. (℃)
6 1 (No. 4 3 1)	165.0~167.0	6 5 (No. 4 4 5)	amorphous
6 2 (No. 4 3 2)	amorphous	6 6 (No. 4 5 4)	amorphous
6 3 (No. 4 3 3)	139.0~145.0	6 7 (No. 4 8 9)	158.0~159.5
6 4 (No. 4 3 4)	147.0~150.0	6 8 (No. 5 0 1)	191.0~192.0

In Table 6, the compounds in Examples 7, 9, 10, 11, 12, 13, 14, 15, 28, 34, 41, 43, 44, 47, 48, 49, 50, 56, 57, 58, 59, 65 and 66 are R compounds, the compound in Example 61 is an S compound, and the compounds in Examples 62, 63, 64, 67 and 68 are RS compounds. The compound in Example 8 is a hydrochloride and that in Example 59' is a fumarate.

Example 69

Synthesis of (R)-4-(1-phenylethylamino)-7-(2-thienyl)thieno[2,3-d]pyridazine (Compound No. 523 in Table 2)

2.0 g of 2-(3-thienyl)-4,4-dimethyloxazoline was dissolved in 50 mℓ of ether, and 10 mℓ of s-butyllithium (1.3 M, cyclohexane solution) was added dropwise thereto at -70°C. The solution was stirred for 1 hour. The reaction solution was added dropwise to a solution of 2.4 g of 2-thenoyl chloride in 50 mℓ of tetrahydrofuran at -78°C, and the solution was stirred for 30 minutes. Thereafter, 1 mℓ of methanol was added to the solution, and the reaction solution was concentrated. After adding water thereto, the solution was extracted with chloroform. The chloroform layer was dried and concentrated, and the residue was purified by silica gel chromatography to obtain 2.8 g of 2-(2-thenoyl)-3-(4,4-dimethyl-2-oxazoline-2-yl)-thiophene.

2.8 g of 2-(2-thenoyl)-3-(4,4-dimethyl-2-oxazoline-2-yl)thiophenewas added to a solution of 30 mℓ of concentrated hydrochloric acid, 20 mℓ of water and 20 mℓ of dioxane, and the solution was stirred at 100°C for 8 hours. After cooling the solution, an aqueous NaCℓ solution was added thereto. The resultant solution was extracted with chloroform and dried. After the solvent was distilled off, the residue was purified by silica gel chromatography to obtain 0.70 g of 2-(2-thenoyl)-3-thiophene carboxylic acid.

0.70 g of 2-(2-thenoyl)-3-thiophene carboxylic acid and 0.22 g of hydrazine hydrate were dissolved in 20 mℓ of ethanol, and the solution was refluxed for 5 hours. After cooling the solution, it was crystallized by adding ether, thereby obtaining 0.61 g of 7-(2-thienyl)thieno[2,3-d]pyridazine-4(5H)-one.

0.30 g of 7-(2-thienyl)thieno[2,3-d]pyridazine-4(5H)-one and 0.30 g of phosphorus oxychloride were dissolved in 10 mℓ of dichloroethane, and the solution was stirred at 100°C for 10 hours. The reaction solution was concentrated, and a 1-N aqueous KOH solution was added thereto under cooling with ice. The solution was extracted with chloroform and dried. The solvent was distilled off, thereby obtaining 0.31 g of 4-chloro-7-(2-thienyl)thieno[2,3-d]pyridazine.

0.31 g of 4-chloro-7-(2-thienyl)thieno[2,3-d]pyridazine and 0.48 g of (R)-1-phenylethylamine was dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 150°C for 10 hours. After cooling the solution, an aqueous 5% KOH solution was added thereto, and the solution was extracted with chloroform and dried. The solvent was distilled off, and the residue was purified by silica gel chromatography to obtain 0.27 g of (R)-4-(1-phenylethylamino)-7-(2-thienyl)-thieno[2,3-d]pyridazine.

Melting point: 215.5 to 216.5°C.

Examples 70 to 94

Compounds of Examples 70 to 94 shown in Tables 7, 8 and 9 were synthesized in accordance with the method in Example 69.

Table 7

Comp. of Ex. No. (Comp. No. in Table2)	m. p. (°C)
7 0 (No. 5 1 3)	187.5~188
7 1 (No. 5 1 4)	162 ~163
7 2 (No. 5 1 5)	205 ~206
7 3 (No. 5 1 6)	184 ~186
7 4 (No. 5 1 7)	183 ~184.5
7 5 (No. 5 1 8)	165.0~166.0
7 6 (No. 5 1 9)	amorphous
7 7 (No. 5 2 0)	amorphous
7 8 (No. 5 2 1)	154.5~156.0
7 9 (No. 5 2 2)	89.0~ 95.0
8 0 (No. 5 2 4)	215.5~216.5
8 1 (No. 5 2 5)	

Table 8

Comp. of Ex. No. (Comp. No. in Table3)	m. p. (°C)
8 2 (No. 5 2 6)	82 ~ 85
8 3 (No. 5 2 7)	
8 4 (No. 5 2 8)	
8 5 (No. 5 2 9)	
8 6 (No. 5 3 0)	140 ~147
8 7 (No. 5 3 1)	130 ~132
8 8 (No. 5 3 2)	129 ~130
8 9 (No. 5 3 3)	130 ~132
9 0 (No. 5 3 4)	amorphous
9 1 (No. 5 3 5)	78 ~ 85
9 2 (No. 5 3 6)	amorphous

In Tables 7 and 8, the compounds in Examples 70, 75, 78, 79, 82, 88, 90, 91 and 92 are R compounds, and the compound in Example 83 is an S compound.

Table 9

Comp. of Ex. No. (Comp. No. in Table4)	m.p. (°C)
9 3 (No. 5 3 7)	172 ~175
9 4 (No. 5 3 8)	152 ~154

In Table 9, the compounds in Examples 93 and 94 are R compounds.

Example 95

Synthesis of (R)-4-(1-cyclohexylethylamino)-7-phenylfurano[2,3-d]pyridazine (Compound No. 539 in Table 5)

5.96 g of diisopropylamine was dissolved in 50 mℓ of tetrahydrofuran, and 35 mℓ of n-butyllithium (1.6 M) was added dropwise thereto at 0°C, and then a solution of 3.0 g of 3-furoic acid in 20 mℓ of tetrahydrofuran was added dropwise thereto at -78°C. The reaction solution was added dropwise to a solution of 5.6 g of benzoyl chloride in 50 mℓ of tetrahydrofuran at -78°C, and the resultant solution was stirred for 30 minutes. After diluted hydrochloric acid was added, the mixed solution was extracted with chloroform and the extract was purified by silica gel chromatography to obtain 3.2 g of 2-benzoyl-3-froic acid.

3.0 g of 2-benzoyl-3-froic acid and 0.76 g of hydrazine hydrate were dissolved in 30 mℓ of ethanol, and the solution was refluxed for 3 hours. After cooling the solution, it was concentrated, and the residue was purified by silica gel chromatography to obtain 0.25 g of 7-phenyl-furano[2,3-d]pyridazine-4-(5H)-one.

0.15 g of 7-phenyl-furano[2,3-d]pyridazine-4-(5H)-one and 10 mℓ of phosphorus oxychloride were dissolved in 10 mℓ of dichloroethane, and the solution was stirred at 100°C for 3 hours. The reaction solution was concentrated, and a 1-N aqueous KOH solution was added thereto under cooling with ice. The solution was extracted with chloroform and dried. The solvent was distilled off, thereby obtaining 0.10 g of 4-chloro-7-phenyl-furano[2,3-d]pyridazine.

0.10 g of 4-chloro-7-phenyl-furano[2,3-d]pyridazine and 0.165 g of (R)-1-cyclohexylethylamine was dissolved in 1 mℓ of N-methylpyrrolidone, and the solution was stirred at 140 °C for 6 hours. After cooling the solution, an aqueous 5% KOH solution was added thereto, and the solution was extracted with chloroform. By purifying the extract by silica gel chromatography, 0.061 g of (R)-4-(1-cyclohexylethylamino)-7-phenyl-furano[2,3-d]pyridazine was obtained.

Melting point: 126 to 130 °C.

Experiment 1

Inhibitory effects of 3,6-disubstituted pyridazine derivatives on platelet agglutination of rats ex vitro

Arterial blood of a rat was centrifuged to obtain platelet rich plasma. 5 mℓ of a medicinal solution was added to 250 μℓ of the platelet rich plasma, and the mixture was incubated for 2 minutes. Thereafter, 3 μg of collagen (produced by Hormon-Chemie) was added to the mixture as a platelet agglutination inducer, and changes in the platelet agglutination were observed and recorded by a 2-channel platelet agglutination degree measuring instrument (Model DP247E, produced by Sienco) for 10 minutes.

The platelet agglutination inhibitory ratio was calculated from the following formula:

Inhibitory ratio = (Tc - Ts)/Tc × 100

Tc: Agglutination degree when only a solvent was added

Ts: Agglutination degree when a medicinal solution was added

The inhibitory ratios of each compound having different mol concentrations are shown in Tables 10 to 14.

Experiment 2

Inhibitory effects of 3,6-disubstituted pyridazine derivatives on platelet agglutination of rats in vivo (oral administration)

A rat group consisting of 8 male Wistar-ST rats each weighing about 250 g was tested. Each compound was suspended in aqueous 1% tragacanth solution. The thus-prepared suspension was orally administered to each rat at a dose of 4 mℓ/kg. One hour after, blood was collected from each carotid artery through a cannula into a plastic test tube containing 3.8% sodium citrate in amount corresponding to 1/10 of the volume of the test tube) and the mixture was stirred. Thereafter, the mixture was centrifuged at 200 × g rpm for 15 minutes, and the supernatant liquid was taken as platelet rich plasma (PRP). The residue was further centrifuged at 2000 × g rpm for 15 minutes, and the supernatant liquid was collected as platelet poor plasma (PPP) and used for measurement of the platelet agglutinating ability. The platelet agglutinating ability was measured by a 2-channel platelet agglutination degree measuring instrument (Model DP247E, produced by Sienco), and recorded by a 2-pen recorder.

Collagen (produced by Hormon-Chemie) having a concentration of 7 to 10 μg/mℓ was used as a platelet agglutination inducer.

The platelet agglutination inhibitory ratio was calculated from the following formula:

Inhibitory ratio = (A - B)/A × 100 (%)

A: Agglutination degree in the group (controlled group) to which only a solution of 1% tragacanth was administered

B: Agglutination degree in the group to which the tragacanth solution containing a compound was administered

The results are shown in Tables 10 to 14.

Table 10

Comp. of Ex. No. (Comp. No. in Table1)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio(%)(p. o)
	10^{-7}M	3×10^{-7}M	10^{-6}M	1 mg/kg
1 (No.1)	89.2	97.1		
2 (No.2)	56.0	96.0		
3 (No.34)		18.4	100	
4 (No.44)		100		
5 (No.40)			51.8	
6 (No.58)	35.2	58.3	98.0	
7 (No.23)	96.1			
9 (No.67)			23.8	
10 (No.75)			36.8	
11 (No.91)			56.2	
12 (No.316)			17.9	
13 (No.329)			22.5	
14 (No.301)		8.2	75.8	
15 (No.331)		13.5	88.1	
16 (No.161)	30.8	32.7	100	
17 (No.162)	27.5	80.4	100	
18 (No.167)	100			10.5
19 (No.177)	46.9	100		
20 (No.178)	100			48.9
21 (No.168)	100			42.5
22 (No.174)	100			38.5
23 (No.169)	100			15.3
24 (No.170)	100			41.5
25 (No.173)	0	5	57.5	
26 (No.150)	100			38.5
27 (No.152)	100			53.6
28 (No.115)	100			
29 (No.116)	100			56.2

Table 10 (continued)

Comp. of Ex. No. (Comp. No. in Table1)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio(%)(p.o)
	10^{-7}M	3×10^{-7}M	10^{-6}M	1 mg/kg
30 (No.118)	68.0	94.6		
31 (No.120)		52.2	91.0	
32 (No.131)	52.5	73.6	88.5	
33 (No.125)		14.6	78.9	
34 (No.137)	98.6			
35 (No.138)	47.6	97.7		
36 (No.141)	49.6	85.1		
37 (No.142)		49.4	73.6	
38 (No.147)	49.4	92.6		
39 (No.207)	94.9			
40 (No.208)	91.2	100		
41 (No.181)	55.8	91.3		
42 (No.189)	96.3			
43 (No.197)		55.0	85.8	
44 (No.215)		16.2	52.6	
45 (No.237)	98.6			
46 (No.241)		40.6	66.5	
47 (No.354)		28.6	91.5	
48 (No.346)	62.7	91.9		25.3
49 (No.362)		81.4	92.1	
50 (No.370)		37.6	94.5	
51 (No.371)			13.4	
52 (No.373)			0.4	
53 (No.375)			8.5	
54 (No.386)			35.5	
55 (No.380)			10.1	
56 (No.396)			3.8	
57 (No.403)			44.1	

Table 10 (continued)

Comp. of Ex. No. (Comp. No. in Table 1)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio (%)(p. o)
	10^{-7}M	3×10^{-7}M	10^{-6}M	1 mg/kg
58 (No410)			2.5	
59 (No293)			27.7	
60 (No431) (R)	94.3			51.3
61 (No431) (S)	30.2	94.4		
62 (No432)		61.3	83.5	
63 (No433)		90.3		
65 (No445)	93.2			
67 (No489)	61.0			41.1
68 (No501)	95.0			

In Table 10, the compounds in Examples 1, 7, 9, 10, 11, 12, 13, 14, 15, 28, 34, 39, 41, 42, 43, 44, 45, 47, 48, 49, 50, 56, 57, 58, 59, 60 and 65 are R compounds, the compound in Example 61 is an S compound, and the compounds in Examples 62, 63, 67 and 68 are RS compounds.

Table 11

Comp. of Ex. No. (Comp. No. in Table 2)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio (%)(p. o)
	10^{-7}M	3×10^{-7}M	10^{-6}M	1 mg/kg
69 (No. 523)	50.8	95.2		
70 (No. 513)	95.2			
71 (No. 514)	30.7	98.6		
72 (No. 515)	5.1	95.3		
73 (No. 516)	42.8	95.6		
74 (No. 517)	73.4	93.5		
75 (No. 518)	94.5			50.2
79 (No. 522)		6.6	94.3	
80 (No. 524)	100			
81 (No. 525)	100			

In Table 11, the compounds in Examples 69, 70, 75 and 79 are R compounds.

Table 12

Comp. of Ex. No. (Comp. No. in Table 3)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio (%)(p. o)
	10^{-7}M	3 x 10^{-7}M	10^{-6}M	1 mg/kg
8 2 (No. 5 2 6)	93.3			37.9
8 3 (No. 5 2 7)		94.3		
8 4 (No. 5 2 8)		24.5	61.6	
8 5 (No. 5 2 9)			40.7	
8 6 (No. 5 3 0)		78.2	90.2	
8 7 (No. 5 3 1)			18.0	
8 9 (No. 5 3 3)		49.5	95.4	
9 0 (No. 5 3 4)	32.7	94.4		60.6

In Table 12, the compounds in Examples 82 and 90 are R compounds, and the compound in Example 83 is an S compound.

Table 13

Comp. of Ex. No. (Comp. No. in Table 4)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio (%)(p.o)
	10^{-7}M	3 x 10^{-7}M	10^{-6}M	1 mg/kg
9 3 (No. 5 3 7)		9.3	93.4	

In Table 13, the compound in Example 93 is an R compound.

Table 14

Comp. of Ex. No. (Comp. No. in Table 5)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio (%)(p.o)
	10^{-7}M	3 x 10^{-7}M	10^{-6}M	1 mg/kg
9 5 (No. 5 3 9)	94.4	100		63.1

In Table 14, the compound in Examples 95 is an R compound.

Experiment 3

Effects of 3,6-disubstituted pyridazine derivatives on on the myocardial infarction of a rat induced by the ligation of the left coronary artery

A rat group consisting of 8 male SD rats each weighing 200 to 250 g was tested. Myocardial infarction was produced in accordance with a method of Selye et al. That is, each rat was fixed on an operating boar on its back, and an about 1.5 cm incision had been made through the skin along the left sternal border under weak etherization. The pericardium was broken to exteriorize the heart, and the left coronary artery was ligated at a position of 1 to 2 mm apart from the origin thereof with black blade 4-O silk suture (produced by Hama Ika Kogyo). Thereafter, the heart was restored to its original position and the chest was sutured. The air in the throacic cavity was discharged by pressing both side breast portions. After the resumption of respiration, the ST elevation in the standard limb lead II by an electrocardiograph (Model ECG-6601, produced by Nihon Koden Co.,). 24 hours after the ligation, blood was collected from the aortas at the abdomen. A fatal amount of blood was then drawn from each rat. The heart was taken out, and a tissue slice (about 2 mm thick) having an annular cross section was cut from the central portion of the heart. The tissue slice was incubated in 20 mℓ of 1% TTC (tryphenyl tetrazolium chloride, produced by Wako Pure Chemical Industries Limited) dissolved in 0.09 M of phosphoric acid buffer (pH 8.6) at 37°C for 20 minutes while shielding light. The tissue slice was photographed by a stereoscopic microscope to produce

a color slide. The image of the tissue slice was projected on a wall surface from the color slide. The cut surface, the infarcted portion (portion not dyed with TTC) and the non-infarcted portion (portion dyed with TTC) were traced on a sheet, and the area of the infarcted portion in the whole cross section was calculated. The medicine was suspended in an aqueous 1% tragacanth solution and orally administered to each rat 60 minutes before the ligation of the left coronary artery.

The myocardial infarction inhibitory ratio was calculated from the following formula:

$$\text{Inhibitory ratio} = \frac{A - B}{A} \times 100\ (\%)$$

A: Infarction degree in the group (controlled group) to which only a solution of 1% tragacanth was administered

B: Infarction degree in the group to which the tragacanth solution containing a medicine was administered

The results are shown in Table 15.

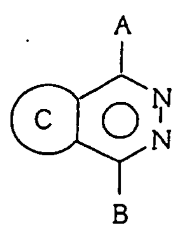
Table 15

Compounds No. (table 1,2,3 and 4)	doses (mg/kg)	percentage of inhibition
4 3 1 (R)	1 3	6 8.5 8 2.2
Aspirin* Ticlopidine*	1 0 0 3 0	1 0.7 1 0.1

* ;anti-platelet aggregation agents

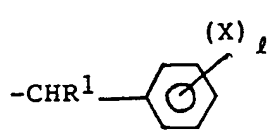
Claims

1. A 3,6-disubstituted pyridazine derivative represented by the following general formula (I), an optical antipode thereof and a pharmaceutically acceptable acid-addition salt thereof:

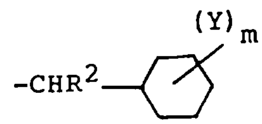


... (I)

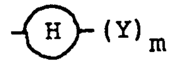
wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a phenyl group, a thienyl group, a furyl group, a thiazolyl group, a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms, a phenylthio group, a nitrogen-containing saturated cyclic group, a pyridyl group or an imidazolyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



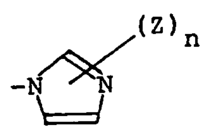
(wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms,
and ℓ represents an integer of 0 to 3),



(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6);

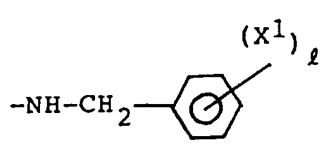


(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cycloalkyl group having 5 to 8 carbon atoms or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or



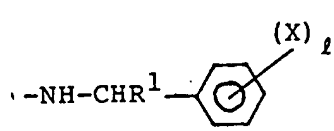
(wherein Z independently represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 to 2); and the ring C represents a benzene ring; a furan ring; or a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms,
provided that the following compounds (1) to (4) are excluded:

(1) compounds represented by the formula (I) wherein A represents a non-substituted imidazolyl group, the ring C represents a benzene ring, and B represents



(wherein X_1 independently represents a halogen atom or an alkyl group having 1 to 4 carbon atoms, and ℓ is as defined above), or an alkylamino group having 3 to 8 carbon atoms;

(2) compounds represented by the formula (I) wherein A represents a phenyl group which may have a substituent, the ring C represents a benzene ring, and B represents



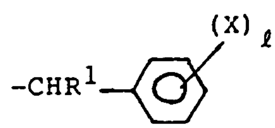
(wherein R^1, X and ℓ are as defined above);

(3) compounds represented by the formula (I) wherein A represents a non-substituted phenyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon

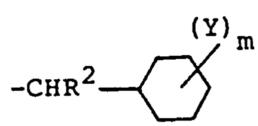
atoms; and

(4) compounds represented by the formula (I) wherein A represents a pyridyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon atoms.

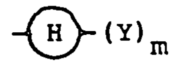
2. A compound according to claim 1, wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a thienyl group, a furyl group, a thiazolyl group, a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms; a phenylthio group; a nitrogen-containing saturated cyclic group or an imidazolyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 3 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



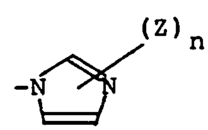
(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents an integer of 0 to 3),



(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6),



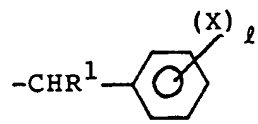
(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above), or an alkyl group having 3 to 8 carbon atoms]; or



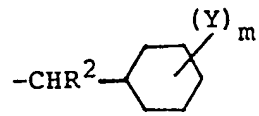
(wherein Z independently represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 to 2); and the ring C represents a benzene ring.

3. A compound according to claim 1, wherein A represents a phenyl group which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cycloalkyl group having 5 to 8 carbon atoms)]; and the ring C represents a benzene ring.

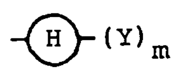
4. A compound according to claim 1, wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; or a phenyl group, a thienyl group or a pyridyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 3 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



(wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents an integer of 0 to 3),

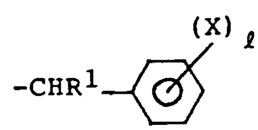


(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6), or

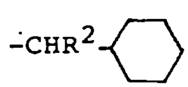


(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above); and the ring C represents a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms.

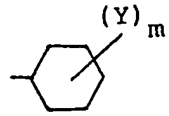
5. A compound according to claim 1, wherein A represents a phenyl group which may be substituted by an alkyl group having 1 to 4 carbon atoms, a chlorine atom or an alkoxy group having 1 to 4 carbon atoms; an alkyl group having 3 to 6 carbon atoms; a cyclohexyl group; a thiazolyl group; a phenoxy group; a phenylthio group; a pyrrolidinyl group; a piperidyl group; a morpholinol group; a pyridyl group; a benzyl group which may be substituted by a halogen atom; or a thienyl group, a furyl group or an imidazolyl group each of which may be substituted by an alkyl group having 1 to 3 carbon atoms; B represents -NH-D [wherein D represents



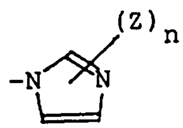
(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X represents a chlorine atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents 0 or 1),



(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms),



(wherein Y independently represents an alkyl group having 1 to 4 carbon atoms or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represent an integer of 0 to 6), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cyclohexyl group or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or

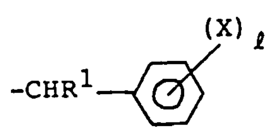


(wherein Z represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 or 1); and the ring C represents a benzene ring, or a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms,
provided that the following compounds (1) and (2) are excluded:

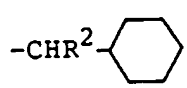
(1) compounds represented by the formula (I) wherein A is a phenyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring; and

(2) compounds represented by the formula (I) wherein A is a pyridyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring.

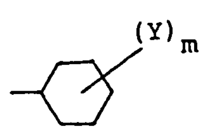
6. A compound according to claim 1, wherein A represents a phenyl group which may be substituted by an alkyl group having 1 to 4 carbon atoms, a chlorine atom or an alkoxy group having 1 to 4 carbon atoms; an alkyl group having 3 to 6 carbon atoms; a cyclohexyl group; a thiazolyl group; a pyrrolidinyl group; a piperidyl group; a morpholinol group; or a thienyl group, a furyl group or an imidazolyl group each of which may be substituted by an alkyl group having 1 to 3 carbon atoms; B represents -NH-D [wherein D represents



(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X represents a chlorine atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents 0 or 1),

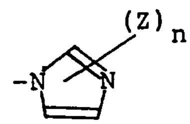


(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms),



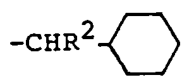
(wherein Y independently represents an alkyl group having 1 to 4 carbon atoms or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an

alkyl group having 1 to 3 carbon atoms, and m represent an integer of 0 to 6), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cyclohexyl group or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or



(wherein Z represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 or 1); and the ring C represents a benzene ring; or a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms,
provided that compounds represented by the formula (I) wherein A is a phenyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring are excluded.

7. A compound according to claim 1, wherein A represents a phenyl group; or a furyl group or a thienyl group each of which may be substituted by an alkyl group having 1 to 4 carbon atoms; and B represents -NH-D [wherein D represents



(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms)].

8. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition for a diseases caused by platelet agglutination, said composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition according to claim 9, wherein said disorder caused by platelet agglutination is ischemic heart disease.

11. A pharmaceutical composition according to claim 10 wherein said ischemic heart disease is myocardial infarction.

12. A pharmaceutical composition according to claim 10 wherein said ischemic heart disease is angina pectoris.

13. A pharmaceutical composition according to claim 9, wherein said disorder caused by platelet agglutination is a cerebrovascular disorder.

14. A pharmaceutical composition according to claim 13, wherein said cerebrovascular disorder is cerebral thrombosis.

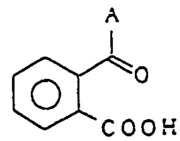
15. A pharmaceutical composition according to claim 13, wherein said cerebrovascular disorder is cerebral embolism.

16. A pharmaceutical composition according to claim 9, wherein said disorder caused by platelet agglutination is a circulation disorder.

17. A pharmaceutical composition according to claim 16, wherein said circulation disorder is a peripheral circulation disorder.

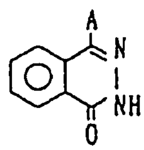
18. A process for the manufacture of the compounds as defined in claims 1 to 7, **characterized by**
(i) when the ring C represents a benzene ring, reacting phthalic anhydride with

(a) a Grignard reagent or a lithium reagent of formula A-M wherein A is as defined in claims 1 to 7 and M represents MgCl, MgBr, MgI or Li or
(b) with a compound of formula A-H wherein A is as defined above to produce a compound of formula (X)



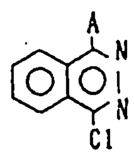
(X)

wherein A is as defined above,
reacting compound (X) with hydrazine or hydrazine hydrate to produce a compound of formula (XI)



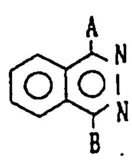
(XI)

wherein A is as defined above,
reacting compound (XI) with a chlorinating agent to provide a compound of formula(XII)



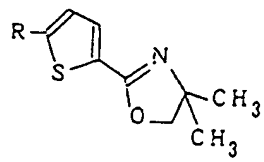
(XII)

wherein A is as defined above.
and reacting compound (XII) with a compound of the formula B-H, wherein B is as defined in claims 1 to 7 to produce a compound of formula (I-a)



(I - a)

wherein A and B are as defined above,
or
(ii) when the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XIII)

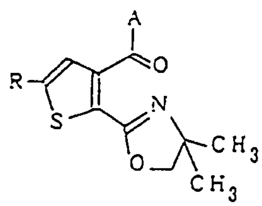


(XIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a base such as butyl lithium to produce an ortho-lithiated compound, which is then reacted with a compound represented by the general formula

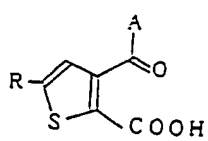
A-COR',

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an imidazolyl group or cyano group to produce a compound of for mula (XIV)



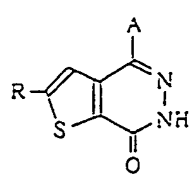
(XIV)

wherein A and R are as defined above,
cleaving the oxazoline ring of compound (XIV) to prepare a compound of formula (XV)



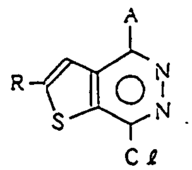
(XV)

wherein A and R are as defined above,
and reacting the compound (XV) with hydrazine or hydrazine hydrate to produce a compound of formula (XVI)



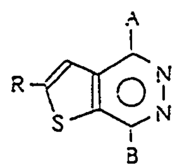
(XVI)

wherein R and A are as defined above,
reacting the compound (XVI) with a chlorinating agent to produce a compound of formula (XVII)



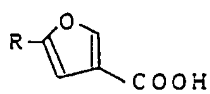
(XVII)

wherein A and R are as defined above and
reacting compound (XVII) with a compound of formula B-H,
wherein B is as defined above to produce a compound of formula (I-b)



(I - b)

wherein A, B and R are as defined above; or
(iii) when the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XVIII)

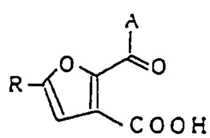


(XVIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a compound of formula (XIX)

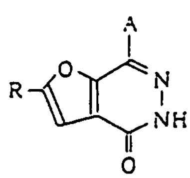
A-COR' (XIX),

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an aryloxy group, an imidazolyl group or a cyano group, to produce a compound of formula (XX)



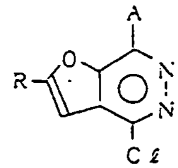
(XX)

wherein R and A are as defined above,
reacting compound (XX) with hydrazine or hydrazine hydrate to produce a compound of formula (XXI)



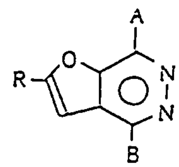
(XXI)

wherein R and A are as defined above,
reacting compound (XXI) with a chlorinating agent to produce a compound of formula (XXII)



(XXII)

wherein A and R are as defined above and
reacting compound (XXII) with a compound of formula B-H, wherein B is as defined above, to produce a compound of formula (I-c)

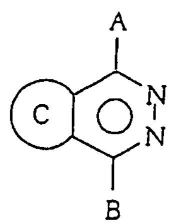


(I - c)

wherein A, B and R are as defined above.

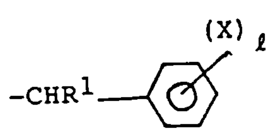
Claim for the following Contracting State : ES

1. A process for the manufacture of a 3,6-disubstituted pyridazine derivative represented by the following general formula (I), an optical antipode thereof and a pharmaceutically acceptable acid-addition salt thereof:

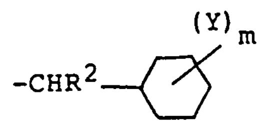


... (I)

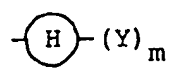
wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a phenyl group, a thienyl group, a furyl group, a thiazolyl group, a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms, a phenylthio group, a nitrogen-containing saturated cyclic group, a pyridyl group or an imidazolyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms; an alkoxy group having 1 to 4 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



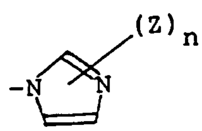
(wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents an integer of 0 to 3),



(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6);

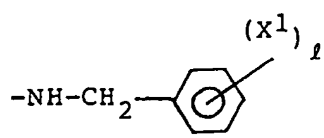


(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above),
$-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cycloalkyl group having 5 to 8 carbon atoms or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or



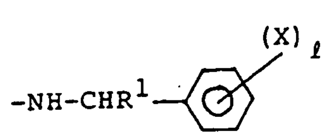
(wherein Z independently represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 to 2); and the ring C represents a benzene ring; a furan ring; or a thiopene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, provided that the following compounds (1) to (4) are excluded:

(1) compounds represented by the formula (I) wherein A represents a non-substituted imidazolyl group, the ring C represents a benzene ring, and B represents



(wherein X_1 independently represents a halogen atom or an alkyl group having 1 to 4 carbon atoms, and ℓ is as defined above), or an alkylamino group having 3 to 8 carbon atoms;

(2) compounds represented by the formula (I) wherein A represents a phenyl group which may have a substituent, the ring C represents a benzene ring, and B represents



(wherein R^1, X and ℓ are as defined above);

(3) compounds represented by the formula (I) wherein A represents a non-substituted phenyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon atoms; and

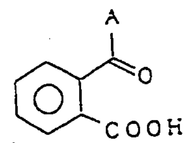
(4) compounds represented by the formula (I) wherein A represents a pyridyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon atoms,

characterized by

(i) when the ring C represents a benzene ring, reacting phthalic anhydride with

(a) a Grignard reagent or a lithium reagent of formula A-M wherein A is as defined above and M represents MgCl, MgBr, MgI or Li or

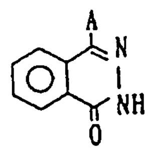
(b) with a compound of formula A-H wherein A is as defined above to produce a compound of formula (X)



(X)

wherein A is as defined above,

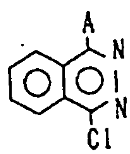
reacting compound (X) with hydrazine or hydrazine hydrate to produce a compound of formula (XI)



(XI)

wherein A is as defined above,

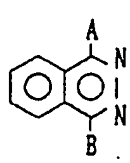
reacting compound (XI) with a chlorinating agent to provide a compound of formula (XII)



(XII)

wherein A is as defined above,

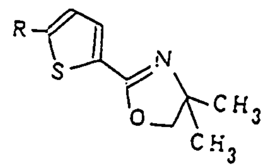
and reacting compound (XII) with a compound of the formula B-H, wherein B is as defined above to produce a compound of formula (I-a)



(I - a)

wherein A and B are as defined above, or

(ii) when the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XIII)

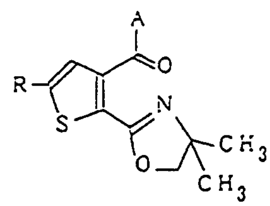


(XIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a base such as butyl lithium to produce an ortho-lithiated compound, which is then reacted with a compound represented by the general formula

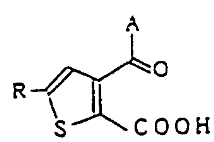
A-COR',

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an imidazolyl group or cyano group to produce a compound of for mula (XIV)



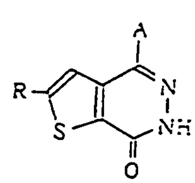
(XIV)

wherein A and R are as defined above,
cleaving the oxazoline ring of compound (XIV) to prepare a compound of formula (XV)



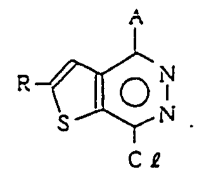
(XV)

wherein A and R are as defined above,
and reacting the compound (XV) with hydrazine or hydrazine hydrate to produce a compound of formula (XVI)



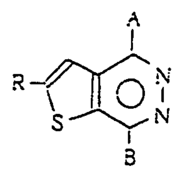
(XVI)

wherein R and A are as defined above,
reacting the compound (XVI) with a chlorinating agent to produce a compound of formula (XVII)



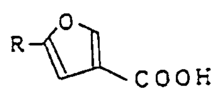
(XVII)

wherein A and R are as defined above and reacting compound (XVII) with a compound of formula B-H, wherein B is as defined above to produce a compound of formula (I-b)



(I - b)

wherein A, B and R are as defined above; or
(iii) when the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XVIII)

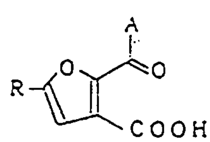


(XVIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a compound of formula (XIX)

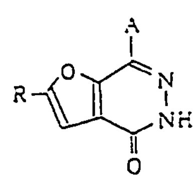
A-COR' (XIX),

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an aryloxy group, an imidazolyl group or a cyano group, to produce a compound of formula (XX)



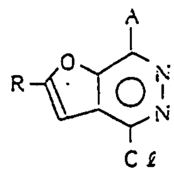
(XX)

wherein R and A are as defined above,
reacting compound (XX) with hydrazine or hydrazine hydrate to produce a compound of formula (XXI)



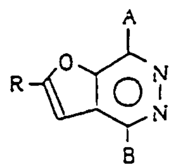
(XXI)

wherein R and A are as defined above,
reacting compound (XXI) with a chlorinating agent to produce a compound of formula (XXII)



(XXII)

wherein A and R are as defined above and
reacting compound (XXII) with a compound of formula B-H, wherein B is as defined above, to produce a compound of formula (I-c)

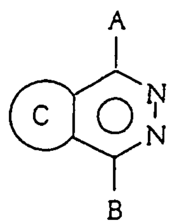


(I - c)

wherein A, B and R are as defined above.

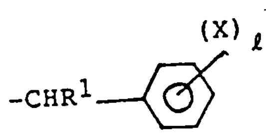
Claims for the following Contracting State : GR

1. A 3,6-disubstituted pyridazine derivative represented by the following general formula (I), an optical antipode thereof and a pharmaceutically acceptable acid-addition salt thereof:

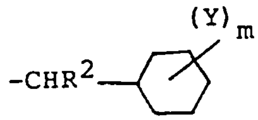


... (I)

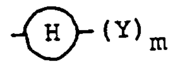
wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a phenyl group, a thienyl group, a furyl group, a thiazolyl group, a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms, a phenylthio group, a nitrogen-containing saturated cyclic group, a pyridyl group or an imidazolyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms; an alkoxy group having 1 to 4 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



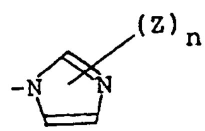
(wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents an integer of 0 to 3),



(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6);

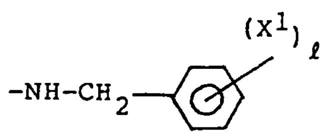


(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above),
$-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cycloalkyl group having 5 to 8 carbon atoms or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or



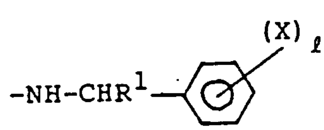
(wherein Z independently represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 to 2); and the ring C represents a benzene ring; a furan ring; or a thiophene ring which maybe substituted by an alkyl group having 1 to 4 carbon atoms, provided that the following compounds (1) to (4) are excluded:

(1) compounds represented by the formula (I) wherein A represents a non-substituted imidazolyl group, the ring C represents a benzene ring, and B represents



(wherein X_1 independently represents a halogen atom or an alkyl group having 1 to 4 carbon atoms, and ℓ is as defined above), or an alkylamino group having 3 to 8 carbon atoms;

(2) compounds represented by the formula (I) wherein A represents a phenyl group which may have a substituent, the ring C represents a benzene ring, and B represents

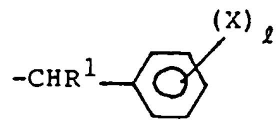


(wherein R^1, X and ℓ are as defined above);

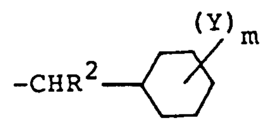
(3) compounds represented by the formula (I) wherein A represents a non-substituted phenyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon atoms; and

(4) compounds represented by the formula (I) wherein A represents a pyridyl group, the ring C represents a benzene ring, and B represents an alkylamino group having 3 to 8 carbon atoms.

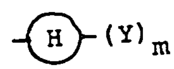
2. A compound according to claim 1, wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; a thienyl group, a furyl group, a thiazolyl group, a phenoxy group, a phenylalkyl group having 7 to 9 carbon atoms; a phenylthio group; a nitrogen-containing saturated cyclic group or an imidazolyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 3 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



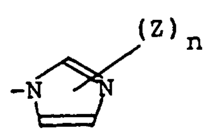
(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents an integer of 0 to 3),



(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6),



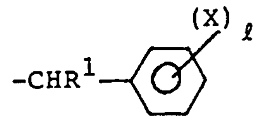
(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above), or an alkyl group having 3 to 8 carbon atoms]; or



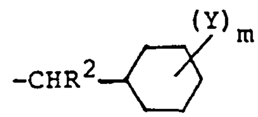
(wherein Z independently represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 to 2); and the ring C represents a benzene ring.

3. A compound according to claim 1, wherein A represents a phenyl group which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cycloalkyl group having 5 to 8 carbon atoms)]; and the ring C represents a benzene ring.

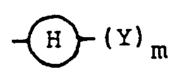
4. A compound according to claim 1, wherein A represents an alkyl group having 3 to 6 carbon atoms; a cycloalkyl group having 5 to 7 carbon atoms; or a phenyl group, a thienyl group or a pyridyl group each of which may have at least one substituent selected from the group consisting of an alkyl group having 1 to 3 carbon atoms and a halogen atom; B represents -NH-D [wherein D represents



(wherein R^1 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, X independently represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents an integer of 0 to 3),

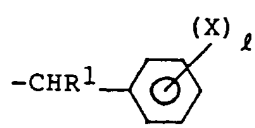


(wherein R^2 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, Y independently represents an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, or any given two Ys combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6), or

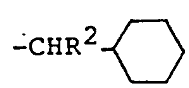


(wherein the ring H represents a cycloalkyl group having 5 to 7 carbon atoms, and Y and m are as defined above); and the ring C represents a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms.

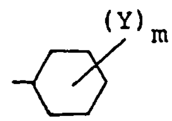
5. A compound according to claim 1, wherein A represents a phenyl group which may be substituted by an alkyl group having 1 to 4 carbon atoms, a chlorine atom or an alkoxy group having 1 to 4 carbon atoms; an alkyl group having 3 to 6 carbon atoms; a cyclohexyl group; a thiazolyl group; a phenoxy group; a phenylthio group; a pyrrolidinyl group; a piperidyl group; a morpholino group; a pyridyl group; a benzyl group which may be substituted by a halogen atom; or a thienyl group, a furyl group or an imidazolyl group each of which may be substituted by an alkyl group having 1 to 3 carbon atoms; B represents -NH-D [wherein D represents



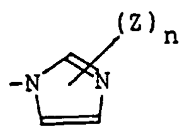
(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X represents a chlorine atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents 0 or 1),



(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms),



(wherein Y independently represents an alkyl group having 1 to 4 carbon atoms or any given two Ys may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cyclohexyl group or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or

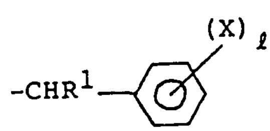


(wherein Z represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 or 1); and the ring C represents a benzene ring, or a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms, provided that the following compounds (1) and (2) are excluded:

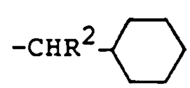
(1) compounds represented by the formula (I) wherein A is a phenyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring; and

(2) compounds represented by the formula (I) wherein A is a pyridyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring.

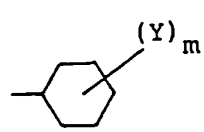
6. A compound according to claim 1, wherein A represents a phenyl group which may be substituted by an alkyl group having 1 to 4 carbon atoms, a chlorine atom or an alkoxy group having 1 to 4 carbon atoms; an alkyl group having 3 to 6 carbon atoms; a cyclohexyl group; a thiazolyl group; a pyrrolidinyl group; a piperidyl group; a morpholino group; or a thienyl group, a furyl group or an imidazolyl group each of which may be substituted by an alkyl group having 1 to 3 carbon atoms; B represents -NH-D [wherein D represents



(wherein R^1 represents an alkyl group having 1 to 4 carbon atoms, and X represents a chlorine atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and ℓ represents 0 or 1),

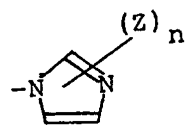


(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms),



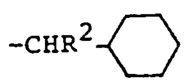
(wherein Y independently represents an alkyl group having 1 to 4 carbon atoms or any given two Ys

may combine to form an alkylene group having 1 to 3 carbon atoms which may be substituted by an alkyl group having 1 to 3 carbon atoms, and m represents an integer of 0 to 6), $-CHR^3R^4$ (wherein R^3 represents an alkyl group having 1 to 5 carbon atoms, and R^4 represents a cyclohexyl group or a thienyl group), or an alkyl group having 3 to 8 carbon atoms]; or



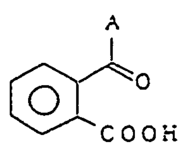
(wherein Z represents an alkyl group having 1 to 4 carbon atoms or a phenyl group, and n represents an integer of 0 or 1); and the ring C represents a benzene ring; or a furan ring or a thiophene ring each of which may be substituted by an alkyl group having 1 to 4 carbon atoms, provided that the compounds represented by the formula (I) wherein A is a phenyl group, B is an alkylamino group having 3 to 8 carbon atoms, and the ring C is a benzene ring are excluded.

7. A compound according to claim 1, wherein A represents a phenyl group; or a furyl group or a thienyl group each of which may be substituted by an alkyl group having 1 to 4 carbon atoms; and B represents -NH-D [wherein D represents



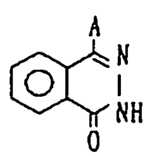
(wherein R^2 represents an alkyl group having 1 to 4 carbon atoms)].

8. A process for the manufacture of the compounds as defined in claims 1 to 7, **characterized by**
   (i) when the ring C represents a benzene ring, reacting phthalic anhydride with
      (a) a Grignard reagent or a lithium reagent of formula A-M wherein A is as defined in claims 1 to 7 and M represents MgCl, MgBr, MgI or Li or
      (b) with a compound of formula A-H wherein A is as defined above to produce a compound of formula (X)



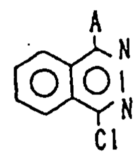
(X)

wherein A is as defined above,
reacting compound (X) with hydrazine or hydrazine hydrate to produce a compound of formula (XI)



(XI)

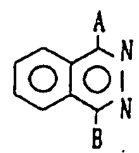
wherein A is as defined above,
reacting compound (XI) with a chlorinating agent to provide a compound of formula (XII)



(XII)

wherein A is as defined above,

and reacting compound (XII) with a compound of the formula B-H, wherein B is as defined in claims 1 to 7 to produce a compound of formula (I-a)

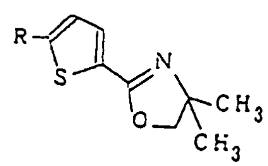


(I - a)

wherein A and B are as defined above,

or

(ii) when the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XIII)

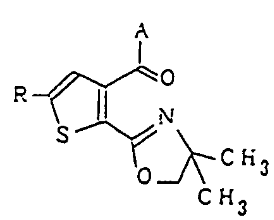


(XIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a base such as butyl lithium to produce an ortho-lithiated compound, which is then reacted with a compound represented by the general formula

A-COR',

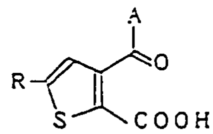
wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an imidazolyl group or cyano group to produce a compound of formula (XIV)



(XIV)

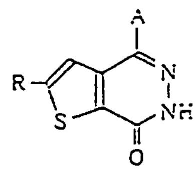
wherein A and R are as defined above,

cleaving the oxazoline ring of compound (XIV) to prepare a compound of formula (XV)



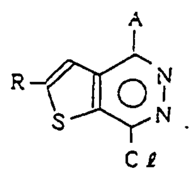
(XV)

wherein A and R are as defined above,
and reacting the compound (XV) with hydrazine or hydrazine hydrate to produce a compound of formula (XVI)



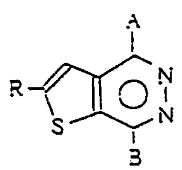
(XVI)

wherein R and A are as defined above,
reacting the compound (XVI) with a chlorinating agent to produce a compound of formula (XVII)



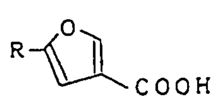
(XVII)

wherein A and R are as defined above and
reacting compound (XVII) with a compound of formula B-H,
wherein B is as defined above to produce a compound of formula (I-b)



(I - b)

wherein A, B and R are as defined above; or
(iii) when the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XVIII)

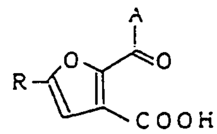


(XVIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a compound of formula (XIX)

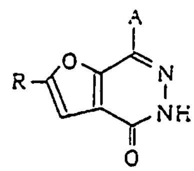
A-COR' (XIX),

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an aryloxy group, an imidazolyl group or a cyano group, to produce a compound of formula (XX)



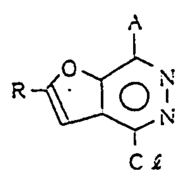
(XX)

wherein R and A are as defined above,
reacting compound (XX) with hydrazine or hydrazine hydrate to produce a compound of formula (XXI)



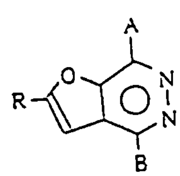
(XXI)

wherein R and A are as defined above,
reacting compound (XXI) with a chlorinating agent to produce a compound of formula (XXII)



(XXII)

wherein A and R are as defined above and
reacting compound (XXII) with a compound of formula B-H, wherein B is as defined above, to produce a compound of formula (I-c)



(I - c)

wherein A, B and R are as defined above.

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EUROPEAN SEARCH REPORT

Application Number

EP 92 11 6413
PAGE1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	DE-A-2 021 195 (ASPRO-NICHOLAS LTD) * page 14 * ---	1,8	C07D237/34 C07D403/04 C07D409/04 C07D409/14 C07D407/04 C07D407/14 C07D417/04 C07D417/14 C07D401/14 C07D401/04 C07D413/04 C07D413/14 C07D409/12 C07D495/04 C07D491/04 A61K31/50
X,D	PATENT ABSTRACTS OF JAPAN vol. 14, no. 356 (C-745)(4299) 2 August 1990 & JP-A-21 29 181 (MORISHITA PHARMACEUT. CO. LTD.) * abstract * ---	1,9	
X,D	PATENT ABSTRACTS OF JAPAN vol. 14, no. 356 (C-745)(4299) 2 August 1990 & JP-A-21 29 182 (MORISHITA PHARMACEUT. CO. LTD.) * abstract * ---	1,9	
A,D	PATENT ABSTRACTS OF JAPAN vol. 14, no. 356 (C-745)(4299) 2 August 1990 & JP-A-21 29 180 (MORISHITA PHARMACEUT. CO. LTD.) * abstract * ---	1,9	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A D	EP-A-0 159 652 (MITSUBISHI YUKA PHARMACEUTICAL CO. LTD.) & JP-A-60 218 377 (MITSUBISHI YUKA YAKUHIN K. K.) ---	1,9	C07D A61K
A,D	PATENT ABSTRACTS OF JAPAN vol. 5, no. 114 (C-64)(786) 23 July 1981 & JP-A-56 53 659 (MITSUBISHI YUKA YAKUHIN K. K.) * abstract * --- -/--	1,9	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14 DECEMBER 1992	FRELON D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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EUROPEAN SEARCH REPORT

Application Number
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PAGE2

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	PATENT ABSTRACTS OF JAPAN vol. 15, no. 293 (C-853)(4821) 25 July 1991 & JP-A-31 06 873 (MORISHITA PHARMACEUT. CO. LTD.) * abstract *	1,9	
A,D	JOURNAL OF MEDICINAL CHEMISTRY vol. 12, no. 3, May 1969, WASHINGTON US pages 555 - 6 H.M. HOLAVA ET AL. * example 11 *	1,8	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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